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HEALTH AND ENVIRONMENTAL EFFECTS DOCUMENT FOR BROMOFORM

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Health and Environmental Effects Documents (HEEDS) are prepared for the Office of Solid Waste and Emergency Response (OSWER). This document series is intended to support listings under the Resource Conservation and Recovery Act (RCRA) as well as to provide health-related limits and goals for emergency and remedial actions under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency Program Office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Several quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference Doses (RfDs) for chronic and subchronic exposures for both the inhalation and oral exposures. In the case of suspected carcinogens, RfDs may not be estimated. Instead, a carcinogenic potency factor, or q_1^*, is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively. Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA.

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PREFACE

Health and Environmental Effects Documents (HEEDs) are prepared for the Office of Solid Waste and Emergency Response (OSWER). This document series is intended to support listings under the Resource Conservation and Recovery Act (RCRA) as well as to provide health-related limits and goals for emergency and remedial actions under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained for Agency Program Office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched for in this document and the dates searched are included in "Appendix: Literature Searched." Literature search material is current up to 8 months previous to the final draft date listed on the front cover. Final draft document dates (front cover) reflect the date the document is sent to the Program Officer (OSWER).

Several quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference doses (RfDs) for chronic and subchronic exposures for both the inhalation and oral exposures. The subchronic or partial lifetime RfD, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval i.e., for an interval that does not constitute a significant portion of the lifespan. This type of exposure estimate has not been extensively used, or rigorously defined as previous risk assessment efforts have focused primarily on lifetime exposure scenarios. Animal data used for subchronic estimates generally reflect exposure durations of 30-90 days. The general methodology for estimating subchronic RfDs is the same as traditionally employed for chronic estimates, except that subchronic data are utilized when available.

In the case of suspected carcinogens, RfDs are not estimated. Instead, a carcinogenic potency factor, or q_1^* (U.S. EPA, 1980b), is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity, and acute mammalian toxicity). Chemical-specific RQs reflect the lowest of these six primary criteria. The methodology for chronic toxicity and cancer based RQs are defined in U.S. EPA, 1984 and 1986, respectively.

EXECUTIVE SUMMARY

Bromoform (CAS number 75-25-2) is a colorless, heavy liquid at room temperature with an odor and taste similar to chloroform (Hawley, 1981). It is sparingly soluble in water but soluble in ethanol, ethyl ether, chloroform, benzene, solvent naphtha and fixed and volatile oils (Hawley, 1981; Stenger, 1978). It is a nonflammable liquid (Hawley, 1981). Bromoform is produced commercially from chloroform by replacement of chloride by reaction with anhydrous aluminum bromide, treatment with bromine and aluminum, or reaction with hydrogen bromide in the presence of an aluminum halide catalyst (Stenger, 1978). Geoliquids, Inc., a division of National Biochemical Co., Chicago, IL, is currently the only domestic manufacturer of this compound (SRI, 1987). Bromoform is used as an intermediate in organic synthesis; in pharmaceuticals as a sedative and antitussive; in gauge fluids; as a solvent for waxes, greases and oils; as an ingredient in fire-resistant chemicals; and as a heavy-dense liquid in solid separations based on differences in specific gravity, such as geological assaying (Stenger, 1978; Hawley, 1981; Verschueren, 1983).

Based on a vapor pressure of 5.6 mm Hg at 25°C (Verschueren, 1983), bromoform is expected to exist primarily in the vapor phase in the atmosphere. Direct photolysis in the troposphere is not expected to be significant because trihalomethanes as a class do not absorb UV radiation at >290 nm (Perwak et al., 1980). Reaction of bromoform with photochemically generated hydroxyl radicals [half-life of 325 days (Atkinson, 1987)] may be one removal mechanism. The likely product of photooxidation of bromoform is $COBr_2$, which may be removed by rain that will hydrolyze it to CO_2 and HBr (Radding et al., 1977). Therefore, bromoform may have a long residence

time in air and may undergo long distance transport. Based on its residence time, <1% of tropospheric bromoform may be transferred to the stratosphere. In water, bromoform will not be expected to adsorb significantly to sediment and suspended solids, or to hydrolyze. Biodegradation of bromoform in water under aerobic and anaerobic conditions may be a significant removal process based on the results of laboratory screening tests. Volatilization from water is expected to be a significant loss process. Bromoform is expected to be highly mobile in soil; therefore, it may leach into groundwater. The relatively high vapor pressure of bromoform [5.6 mm Hg (Verschueren, 1983)] suggests that volatilization from dry soil surfaces is likely to be significant. Biodegradation of bromoform in soil and groundwater may be a significant removal process, based on the results of soil percolation studies (Bouwer et al., 1984) and aerobic and anaerobic laboratory screening tests in water. Hydrolysis is not expected to be an important removal process in soil.

Exposure of the general population to bromoform is most likely to occur from ingestion of contaminated drinking water and inhalation of contaminated ambient air. Minor dermal exposure may occur in swimming pools, especially beachfront pools that use salt water. Occupational exposure standards warn of possible significant skin absorption for tribromomethane under industrial exposure conditions (OSHA, 1976), but no evidence in the available literature cited in Appendix A indicates that dermal exposure contributes significantly to the total dose of tribromomethane for the general public (U.S. EPA, 1980a). Bromoform has been found in samples of drinking water, groundwater, surface water, effluent from publicly-owned treatment works, sediment, marine algae and ambient air. The U.S. EPA STORET Data Base (U.S. EPA, 1988) indicates that bromoform was found in samples of sediment (44

total samples) at a concentration range of 0.10-0.025 ppm (wet weight) and an average concentration of 0.014 ppm. Bromoform has been found in several species of algae, but no information regarding its presence in foods was found in the available literature cited in Appendix A.

The acute toxicity of bromoform to freshwater fish was determined for bluegill sunfish and common carp. The 96-hour LC_{50}s for sunfish exposed to bromoform were 29.3 ppm (U.S. EPA, 1978) and 29 mg/ℓ (Buccafusco et al., 1981). The NOEC reported by U.S. EPA (1978) was 13 ppm. Mattice et al. (1981) and Trabalka et al. (1979) reported that the LC_{50} for common carp eggs exposed to bromoform was 52 mg/ℓ. The acute toxicity of bromoform to saltwater fish was determined for menhaden and sheepshead minnow. The 96-hour LC_{50} for menhaden exposed to bromoform was 12 mg/ℓ (Gibson et al., 1979a,b, 1981). The 96-hour LC_{50} for sheepshead minnow exposed to bromoform was 18 ppm in a static test (Heitmuller et al., 1981) and 7.1 mg/ℓ in a flowthrough test (Ward et al., 1981). Heitmuller et al. (1981) reported a NOEC of 2.9 ppm, while U.S. EPA (1978) reported a NOEC for sheepshead minnow exposed to bromoform of 4.83 ppm and a MATC of >4.83 to <8.5 ppm.

The acute toxicity of bromoform to molluscs was reported by Stewart et al. (1979) and Gibson et al. (1979a,b, 1981). Survival among larvae of the American oyster fell from >90 to ~42% at bromoform concentrations from 0-10 mg/ℓ. Inadequate levels of mortality among adult clams and oysters prevented calculation of LC_{50}s for these species.

U.S. EPA (1978) and LeBlanc (1980) reported 48-hour LC_{50}s for Daphnia magna of 46.5 ppm, with a NOEC of <7.8 ppm. The 96-hour LC_{50} for a related species, Daphnia pulex, was 44 mg/ℓ (Trabalka and Burch, 1978). Richie et al. (1984) reported a 24-hour LC_{50} of 75 ppm for larval mosquitoes exposed to bromoform.

The 96-hour LC_{50} for the saltwater crustacean, Mysidopsis bahia, was 24.4 ppm, while the NOEC was reported as 8.67 ppm (U.S. EPA, 1978). Gibson et al. (1979a,b, 1981) reported a 96-hour LC_{50} for shrimp of 26 mg/ℓ. Kerster and Schaeffer (1983) reported that bromoform was not teratogenic to brine shrimp nauplii at concentrations of 0.25-25 ppm.

Ward et al. (1981) reported that bromoform at concentrations of $\leq$15 mg/ℓ had no effect on hatching success or growth of surviving sheepshead minnow juveniles, while concentrations $\geq$8.5 mg/ℓ significantly increased mortality among juveniles, producing an estimated MATC of >4.8 to <8.5.

Anderson et al. (1979), Gibson et al. (1979a,b,c, 1981) and Scott et al. (1980, 1982, 1983) reported that bromoform was bioaccumulated 3- to 50-fold by clams, oysters, shrimp and fish, but that depuration was very rapid (<2-4 days). A BCF value calculated from the log K_{ow} for bromoform also indicates that bromoform does not bioaccumulate significantly.

U.S. EPA (1978) reported 96-hour EC_{50}s for cultures of the freshwater green alga, Selanastrum capricornutum, exposed to bromoform of 112 and 116 ppm, with a NOEC of 28.9 ppm. U.S. EPA (1978) also reported 96-hour EC_{50}s for cultures of the saltwater alga, Skeletonema costatum, exposed to bromoform of 12.3 and 11.5 ppm, with a NOEC of 1.73 ppm.

Bromoform is absorbed through the respiratory tract, skin and gastrointestinal tract (Von Oettingen, 1955), apparently quite readily from the respiratory and gastrointestinal tracts. Once absorbed, bromoform and its metabolites are distributed rapidly, with highest levels located in adipose tissue and blood (Parra et al., 1986). Substantial levels are also found in several other organs including the brain. Elimination occurs rapidly from all tissues including fat (Parra et al., 1986). Metabolism of bromoform occurs predominantly in the liver by a cytochrome P450 oxidase system to CO

and CO_2 (Ahmed et al., 1977, 1980; Stevens and Anders, 1979). Dibromocarbonyl is a likely toxic intermediate in this pathway (NTP, 1988). Mice appear to metabolize bromoform by this pathway more completely than do rats (Mink et al., 1986). Bromoform metabolism depletes liver GSH (Pohl et al., 1980b) because this system is stimulated by sulfhydral compounds (e.g., GSH) (Stevens and Anders, 1979; Ahmed et al., 1980). Bromoform also appears to be metabolized through a reductive pathway that produces free radical intermediates. Excretion of bromoform and its metabolites occurs to a small extent from the urine and to a much larger extent through the lungs in mice, rats (Mink et al., 1986) and rabbits (Lucas, 1928).

The liver, kidneys and central nervous system appear to be important target organs for bromoform toxicity. Both inhalation (Dykan, 1962, 1964) and oral (NTP, 1988; Chu et al., 1982a,b; Borzelleca, 1983) administration result in aberrations in morphology or function of these organs. Hepatocellular vacuolization was found in both male mice ($\geq$200 mg/kg/day) and male rats ($\geq$50 mg/kg/day) in a subchronic study (13 weeks, 5 days/week) and in female mice ($\geq$100 mg/kg/day) in a chronic study (103 weeks, 5 days/week) sponsored by NTP (1988). Compound-related mortality was observed in male rats (200 mg/kg/day) in the chronic study. Also, narcosis (Sax, 1984) and lethargy (Bowman et al., 1978; Chu et al., 1980; NTP, 1988) were observed in animals receiving bromoform by inhalation and oral routes, respectively. Altered RES function was observed in male and female mice receiving bromoform at a level of 125 mg/kg/day for 90 days by gavage (Munson et al., 1977, 1978). Operant behavior was impaired after administration of bromoform to mice at levels of 100 and 400 mg/kg/day for 60 days (Balster and Borzelleca, 1982).

NTP (1988) concluded that there was "some evidence of carcinogenicity of bromoform for male F344/N rats and clear evidence...for female F344/N rats."

Female rats at 200 mg/kg/day displayed a higher incidence of neoplastic lesions of the large intestine compared with male rats and untreated controls (NTP, 1988). This may be due in part to the fact that male rats had reduced survival rates compared with females at equal doses (NTP, 1988). In another study (Theiss et al., 1977) bromoform produced an increase in the number of pulmonary adenomas per mouse in strain A mice following intraperitoneal administration. Bromoform tested positive for mutagenicity in both *in vivo* and *in vitro* assays (NTP, 1988). Bromoform did not produce teratogenic effects or maternal toxicity, but did produce fetotoxic effects in rats treated at 100, but not at 50 mg/kg/day (Ruddick et al., 1983).

A subchronic oral RfD of 0.2 mg/kg/day was derived by applying an uncertainty factor of 100 to the NOEL of 17.9 mg/kg/day in rats in the NTP (1988) 13-week gavage study. Hepatocellular vacuolization occurred at higher doses. The subchronic oral RfD was used as the basis for the chronic oral RfD of 0.02 mg/kg/day after an additional subchronic-to-chronic uncertainty factor of 10. A q_1^* of 7.9×10^{-3} $(mg/kg/day)^{-1}$ based on an internal dose was derived from the incidence of tumors in the large intestine of female rats treated by gavage for 2 years (NTP, 1988). This estimate of cancer potency is considered valid for oral exposure. Bromoform is assigned to U.S. EPA weight-of-evidence group B2 - Probable Human Carcinogen.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
ALA	δ-Aminolevulinic acid
BCF	Bioconcentration factor
BUN	Blood urea nitrogen
CO	Carbon monoxide
COX_2	Carbonyl halides
CS	Composite score
DNA	Deoxyribonucleic acid
EC_{50}	Concentration effective to 50% of recipients (and all other subscripted concentration levels)
FMAV	Family mean acute values
GOT	Glutamic oxaloacetic transaminase
GSH	Reduced glutathione
K_{oc}	Soil sorption coefficient standardized with respect to organic carbon
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients (and all other subscripted dose levels)
LDH	Lactate dehydrogenase
LD_{50}	Dose lethal to 50% of recipients
LD_{LO}	Lowest dose lethal to recipients
LOAEL	Lowest-observed-adverse-effect level
LOEL	Lowest-observed-effect level
MATC	Maximum allowable toxicant concentration
MED	Minimum effective dose
MTD	Maximum tolerated dose
NADPH	Nicotinamide adenine dinucleotide phosphate (reduced form)

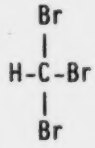
LIST OF ABBREVIATIONS (cont.)

NOAEL	No-observed-adverse-effect level
NOEC	No-observed-effect concentration
NOEL	No-observed-effect level
OZT	2-Oxothiazolidine-4-carboxylic acid
PAH	p-Aminohippuric acid
PEL	Permissible exposure level
ppm	Parts per million
ppb	Parts per billion
ppt	Parts per trillion
RES	Reticuloendothelial system
RfD	Reference dose
RNA	Ribonucleic acid
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
SCE	Sister-chromatid exchange
SDH	Succinic dehydrogenase
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
TLV	Threshold limit value
UV	Ultraviolet
v/v	Volume per volume
w/v	Weight per volume

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Bromoform is the common name for tribromomethane (Stenger, 1978). The structure, molecular weight, empirical formula and CAS Registry number for this compound are as follows:



Molecular weight: 252.77

Empirical formula: $CHBr_3$

CAS Registry number: 75-25-2

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Bromoform is a colorless, heavy liquid at room temperature with an odor and taste similar to chloroform (Hawley, 1981). It is soluble in ethanol, ethyl ether, chloroform, benzene, solvent naphtha and fixed and volatile oils (Hawley, 1981; Stenger, 1978). Bromoform is nonflammable (Hawley, 1981). Under certain conditions, bromoform can undergo nucleophilic substitution reactions; however, the compound is reasonably stable toward chemical reactions under most environmental conditions (Chapter 2).

Selected physical properties are as follows:

Boiling point:	149.5°C	Stenger, 1978
Melting point:	7.7°C	Stenger, 1978
Vapor pressure (25°C):	5.6 mm Hg	Verschueren, 1983
Log K_{OW}:	2.37 (estimated)	U.S. EPA, 1987a
Water solubility (25°C):	3100 mg/ℓ	Horvath, 1982
Specific gravity (20°C):	2.887	Hawley, 1981

Refractive index, n_D^{19}:	1.5980	Stenger, 1978
Odor threshold:		
air	1.3 ppm (v/v)	Amoore and Hautala, 1983
water	0.51 ppm (w/v)	Amoore and Hautala, 1983

1.3. PRODUCTION DATA

In 1977, Dow Chemical Company U.S.A. manufactured between 0.1 and 1.0 million pounds of bromoform, Olin Corp. manufactured between 10 and 100 thousand pounds, and Freeman Industries, Inc., manufactured between 1 and 10 thousand pounds (U.S. EPA, 1977). Rhone-Poulenc, Inc., was reported to be an importer of bromoform in 1977 (U.S. EPA, 1977). SRI (1987) lists Geoliquids, Inc., Division of National Biochemical Co., Chicago, IL, as the only current producer of bromoform.

Bromoform is produced commercially from chloroform by replacement of chloride by reaction with anhydrous aluminum bromide, treatment with bromine and aluminum, or reaction with hydrogen bromide in the presence of an aluminum halide catalyst (Stenger, 1978). After the chlorine is replaced with bromine, the mixture is washed with cold water to remove inorganic materials and the product is distilled (Stenger, 1978). Bromoform also can be produced by heating ethanol or acetone with bromine and alkali hydroxide (Hawley, 1981) or with sodium hypochlorite and a bromide (Stenger, 1978). Bromoform is usually sold with 3-4% ethanol added as a stabilizer (Stenger, 1978).

Bromoform is produced inadvertently during chlorination of potable water and wastewaters as a result of reaction of chlorine with humic substances and naturally-occurring bromide ions present in water (Stenger, 1978).

Bromoform appears to be a natural product in the marine environment; the compound was quantified in several species of algae (Section 3.2.) (Gschwend et al., 1985; Callahan et al., 1979).

1.4. USE DATA

Bromoform is used as an intermediate in organic synthesis; in pharmaceuticals as a sedative and antitussive; in gauge fluids; as a solvent for waxes, greases and oils; as an ingredient in fire-resistant chemicals; and as a heavy-dense liquid in solid separations based on differences in specific gravity, such as geological assaying (Stenger, 1978; Hawley, 1981; Verschueren, 1983).

1.5. SUMMARY

Bromoform (CAS number 75-25-2) is a colorless, heavy liquid at room temperature with an odor and taste similar to chloroform (Hawley, 1981). It is sparingly soluble in water but soluble in ethanol, ethyl ether, chloroform, benzene, solvent naphtha and fixed and volatile oils (Hawley, 1981; Stenger, 1978). It is a nonflammable liquid (Hawley, 1981). Bromoform is produced commercially from chloroform by replacement of chloride by reaction with anhydrous aluminum bromide, treatment with bromine and aluminum, or reaction with hydrogen bromide in the presence of an aluminum halide catalyst (Stenger, 1978). Geoliquids, Inc., a division of National Biochemical Co., Chicago, IL, is currently the only domestic manufacturer of this compound (SRI, 1987). Bromoform is used as an intermediate in organic synthesis; in pharmaceuticals as a sedative and antitussive; in gauge fluids; as a solvent for waxes, greases and oils; as an ingredient in fire-resistant chemicals; and as a heavy-dense liquid in solid separations based on differences in specific gravity, such as geological assaying (Stenger, 1978; Hawley, 1981; Verschueren, 1983).

2. ENVIRONMENTAL FATE AND TRANSPORT

2.1. AIR

Pertinent data regarding the environmental fate and transport of bromoform in air are limited. Whenever possible, information concerning the environmental fate and transport of this compound was derived from physical property data or molecular structure. Based on a vapor pressure of 5.6 mm Hg at 25°C (Verschueren, 1983) and the estimation of Eisenreich et al. (1981), bromoform is expected to exist primarily in the vapor phase in the atmosphere.

2.1.1. Chemical Reactions. Using the method of Atkinson (1987), the rate constant for reaction of bromoform vapor with photochemically produced hydroxyl radicals in the atmosphere has been estimated to be 4.94×10^{-14} cm^3/molecule-sec at 25°C. Based on this value and assuming an average ambient HO• concentration of 5.0×10^5 molecules/cm^3, the half-life for this reaction has been estimated to be 325 days. Although the reaction of bromoform with photochemically produced hydroxyl radicals appears to be slow, the reaction will be a significant removal process if there are no other significant competing removal processes. The likely product of photo-oxidation of bromoform is $COBr_2$, which may be removed by rain that will hydrolyze it to CO_2 and HBr (Radding et al., 1977).

2.1.2. Photolysis. No specific information regarding the rate of photolysis of bromoform in the atmosphere was found in the available literature. Direct photolysis in the troposphere is not expected to be significant because trihalomethanes as a class do not absorb UV radiation at >290 nm (Perwak et al., 1980).

2.2. WATER

2.2.1. Hydrolysis. The reported rate constant for the hydrolysis of bromoform is 3.2×10^{11} sec^{-1} at 25°C and pH 7 (Mabey and Mill, 1978). This corresponds to a half-life of 686 years for hydrolysis of bromoform. From this, it can be concluded that hydrolysis of bromoform is not important in the transformation of this compound in the aqueous environment.

2.2.2. Oxidation. No specific information regarding the oxidation of bromoform under aquatic conditions was found in the available literature.

2.2.3. Adsorption. A K_{oc} of 282 was reported for an unspecified aquifer material (Abdul et al., 1987). A K_{oc} of 100 was estimated using a measured water solubility of 3100 mg/ℓ (Horvath, 1982) and the following linear regression equation (Lyman, 1982):

$$\log K_{OC} = -0.557 \log S + 4.277 \quad (2\text{-}1)$$
$$(S \text{ in } \mu mol/\ell)$$

These K_{oc} values suggest that bromoform would not sorb significantly to sediment and suspended solids.

2.2.4. Volatilization. The volatilization half-lives for bromoform at 25°C in unstirred mineral water solutions at depths of 6.5 cm and 14.5 cm are 23.9 and 65.4 minutes, respectively (Francois et al., 1979). Using a measured Henry's Law constant of 6.6×10^{-4} atm m^3/mol (Hine and Mookerjee, 1975) and the method of Thomas (1982), a half-life of 6.7 hours was estimated for volatilization of bromoform from a river 1 m deep flowing 1 m/sec with a wind velocity of 3 m/sec. Therefore, volatilization is expected to be an important loss process.

2.2.5. Biodegradation. Pertinent data regarding the biodegradation of bromoform in natural waters were not located in the available literature cited in Appendix A.

Bromoform at 5 ppm was inoculated with settled domestic waste-water seed for 7 days, followed by 3 weekly subcultures at 25°C using a static culture flask-screening procedure (Tabak et al., 1981). Percent biodegradation in the original culture, and the first, second and third subcultures were 11, 22, 40 and 48, respectively, indicating that significant degradation might occur with adapted microorganisms and that adaptation was a slow process (Tabak et al., 1981).

Bromoform at an initial concentration of 26 ppb was >99% removed by treatment in a methanogenic (anaerobic conditions) biofilm column after a 2-day detention time in the presence of nitrate as an electron acceptor (Bouwer and McCarty, 1984). Bromoform was not tested in the aerobic biofilm column tests because it was not biodegraded in aerobic batch cultures (Bouwer and McCarty, 1984). Under static anaerobic batch conditions in the presence of nitrate, bromoform at an average concentration of 66 ppb was 11, 44, 47 and 97% degraded after 2, 3, 4 and 6 weeks, respectively (Bouwer and McCarty, 1983).

The above anaerobic degradation data are not consistent with field data obtained from a groundwater recharge project in Palo Alto, CA, in which reclaimed municipal wastewater was injected directly (Rittmann et al., 1980). The bromoform level from the injection well to the observation well (7.6 m between wells) was only slightly attenuated compared with that of tracer chloride ion. Apparently, the bromoform passed through the biologically active zone without being degraded (Rittmann et al., 1980). More recent data from the continuation of these studies, however, suggest presumptive evidence of the degradation of bromoform in recharged groundwater under anaerobic conditions (Roberts et al., 1982). The presence of an electron acceptor in the reclaimed wastewater, such as nitrate, might be necessary for biodegradation to occur.

The relative efficiency of removal of toxic pollutants, including bromoform, from spiked raw wastewater by several wastewater treatment processes was studied by Hannah et al. (1986). The percent removal of bromoform reported with a conventional activated sludge system (residence time of 7.5 hours at design flow), a facultative lagoon system (hydraulic detention time of 25.6 days) and an aerated lagoon system (hydraulic detention time of 6.4 days) was 65, 84 and 80%, respectively (Hannah et al., 1986).

2.3. SOIL

2.3.1. Hydrolysis. Based on available information on the hydrolysis in water, hydrolysis of bromoform is not expected to be significant in the transformation of this compound in soil (see Section 2.2.1.).

2.3.2. Leaching. A K_{oc} of 181 was calculated from a Freundlich K value of 1.54 and a organic carbon content of 0.85% reported for a Keweenaw sandy loam soil (Hutzler et al., 1986). A K_{oc} of 100 was estimated using a measured water solubility of 3100 mg/ℓ (Horvath, 1982), and the linear regression equation of Lyman (1982) (see Equation 2-1). These K_{oc} values suggest that bromoform would be moderately to highly mobile in soil (Swann et al., 1983) and therefore would be expected to leach into groundwater.

2.3.3. Volatilization. The relatively high vapor pressure of bromoform [5.6 mm Hg (Verschueren, 1983)] suggests that volatilization from dry soil surfaces is probably significant. Evaporation from moist soils may also be significant, since bromoform does not have a strong tendency to adsorb to soil and apparently evaporates rapidly from water solutions (see Sections 2.3.4. and 2.2.5.).

2.3.4. Biodegradation. A study of the movement of trace organic pollutants, including bromoform, during rapid infiltration of secondary wastewater for groundwater recharge indicated that the likely cause of the decrease of bromoform during soil percolation was biodegradation (Bouwer et al., 1984).

The renovated wastewater studied contained nitrate, which appears to be necessary as an electron acceptor in the biodegradation process. The degradation of the bromoform may have actually occurred in the area of the groundwater and aquifer material, which was mainly anaerobic (Bouwer et al., 1984).

2.4. SUMMARY

Based on a vapor pressure of 5.6 mm Hg at 25°C (Verschueren, 1983), bromoform is expected to exist primarily in the vapor phase in the atmosphere. Direct photolysis in the troposphere is not expected to be significant because trihalomethanes as a class do not absorb UV radiation at >290 nm (Perwak et al., 1980). Reaction of bromoform with photochemically generated hydroxyl radicals [half-life of 325 days (Atkinson, 1987)] may be one removal mechanism. The likely product of photooxidation of bromoform is $COBr_2$, which may be removed by rain that will hydrolyze it to CO_2 and HBr (Radding et al., 1977). Therefore, bromoform may have a long residence time in air and may undergo long distance transport. Based on its residence time, <1% of tropospheric bromoform may be transferred to the stratosphere. In water, bromoform will not be expected to adsorb significantly to sediment and suspended solids, or to hydrolyze. Biodegradation of bromoform in water under aerobic and anaerobic conditions may be a significant removal process based on the results of laboratory screening tests. Volatilization from water is expected to be a significant loss process. Bromoform is expected to be highly mobile in soil; therefore, it may leach into groundwater. The relatively high vapor pressure of bromoform [5.6 mm Hg (Verschueren, 1983)] suggests that volatilization from dry soil surfaces is likely to be significant. Biodegradation of bromoform in soil and groundwater may be a significant removal process, based on the results of soil percolation studies

(Bouwer et al., 1984) and aerobic and anaerobic laboratory screening tests in water. Hydrolysis is not expected to be an important removal process in soil.

3. EXPOSURE

3.1. WATER

In the U.S. EPA National Organics Reconnaissance Survey (NORS) of 80 cities, bromoform was found in the finished drinking waters of 26 samples (Symons et al., 1975). The concentration of bromoform in these positive samples ranged from 0.0008-0.092 ppm; 93.3% of all the cities tested had a bromoform concentration of <0.005 ppm (Symons et al., 1975). The authors concluded that bromoform was formed as a result of chlorination and that its concentrations were related to the organic content of the water.

In its Region V Organics Survey of 83 sites, the U.S. EPA (1980a) reported that drinking water from 14% of the locations contained detectable levels of bromoform, with a median concentration of 0.001 ppm and a maximum concentration of 0.007 ppm.

The U.S. EPA National Organic Monitoring Survey (NOMS), conducted in three phases during 1976 and 1977, sampled 113 water supplies representing various sources and treatments (U.S. EPA, 1980a). Incidence and concentration data are summarized in Table 3-1.

Data from a Canadian national survey for halomethanes in drinking water are in general agreement with data from the United States (U.S. EPA, 1980a). Samples taken from 70 finished water distribution systems showed bromoform at concentrations ranging from 0-0.2 ppb, with a median concentration of 0.01 ppb.

Data regarding the incidence and concentration of bromoform in finished drinking waters are summarized in Table 3-2.

Using the median values from Table 3-2, an average daily intake can be estimated. The values used represent ~28% positive values out of 945 data points from drinking water plants (Westrick et al., 1984). The average and

TABLE 3-1

Frequency of Occurrence and Concentration of Bromoform in U.S. EPA NOMS Survey of 113 Water Supplies[a]

	Number of Positive Analyses per Number of Analyses			Mean Concentration ppb (Positive Results Only)			Median Concentration ppb (All Results)		
Phase	I	II	III	I	II	III	I	II	III
Q[b]	3/111[c]	6/118	19/106	21[c]	28	13	3-5[d]	3[d]	0.2-0.6[d]
T[b]		38/116	30/105	NA	12	13	NA	3[d]	0.3-0.6[d]

[a]Source: U.S. EPA, 1980a

[b]Quenched (Q) samples were preserved with sodium thiosulfate at sampling, shipped at ambient temperature and stored at 20-25°C 3-6 weeks before analyses. Terminal (T) samples were treated similarly to Q except there was no sodium thiosulfate treatment.

[c]Samples were shipped iced and were stored refrigerated 1-2 weeks before analyses.

[d]Minimum quantifiable limits.

NA = Not applicable

TABLE 3-2

Summary of Frequency of Occurrence and Concentration Data for Bromoform in Finished Water from Drinking Water Treatment Plants

Location (year)	Number of Plants	Number of Samples	% Plants Positive	Range (ppb)	Median (ppb)	Mean (ppb)	Reference
Michigan	40	NR	7.5	ND	ND	0.1	Furlong and Ditri, 1986
Canada (1975)	70	NR	NR	ND-2.1	NR	0.1	Williams et al., 1980
Canada (1979)	30	30 August-September	13	ND-2	NR	<1	Otson et al., 1982
Canada (1979)	30	30 August-September	10	ND-1	NR	<1	Otson et al., 1982
Canada (1979)	30	30 November-December	3.3	ND-1	NR	<1	Otson et al., 1982
Great Lakes, Canada (1982)	10	14 summer	ND	ND	ND	ND	Otson, 1987
Great Lakes, Canada (1983)	10	14 winter	ND	ND	ND	ND	Otson, 1987
Great Lakes, Canada (1983)	10	14 spring	11[f]	NR	NR	0.1	Otson, 1987
Philadelphia, PA (1975-1976)	3	6	100	NR	NR	NR	Suffet et al., 1980
Iowa	18	NR	50	1.0-10	NR	NR	Kelley, 1985
United States[a]	NR	NR	36.3	NR	NR	NR	Dyksen and Hess, 1982
United States[a,b]	280[c]	NR	15.7	ND-54	2.4	NR	Westrick et al., 1984
United States[a,b]	186[d]	NR	30.6	ND-50	3.8	NR	Westrick et al., 1984
United States[a,e]	321[c]	NR	27.4	ND-110	3.7	NR	Westrick et al., 1984
United States[a,e]	158[d]	NR	38.0	ND-68	5.1	NR	Westrick et al., 1984

[a]Finished drinking water from groundwater supplies
[b]Randomly selected sites
[c]Systems serving <10,000 persons
[d]Systems serving >10,000 persons
[e]Non-randomly selected sites
[f]11% of 14 samples positive; number of plants positive NR.
NR = Not reported; ND = not detected

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range of the median values are 3.8 and 2.1-5.1 ppb, respectively (Westrick et al., 1984). Using the average median value of 3.8 ppb, an estimated average daily intake of 7.6 µg is obtained, assuming an average consumption of 2 ℓ of drinking water/day.

A survey of groundwaters in New Jersey from 1977-1979 found bromoform in 22% of 1072 samples tested (Page, 1981); concentrations ranged from 0.1 ppb (minimum reportable concentration) to 34.7 ppb (Burmaster, 1982). Bromoform was detected in groundwater from Delaware at a concentration of 20 ppb (Rao et al., 1985), and in groundwater from the Netherlands at a maximum concentration of 4 ppb (Zoeteman et al., 1981).

Bromoform was detected in 3% of 204 water samples collected near industrial sites in the United States (Helz, 1980). A survey of surface waters in New Jersey from 1977-1979 found bromoform in 32.6% of 604 sites, with a maximum reported concentration of 3.7 ppb (Page, 1981). Bromoform concentrations in the Iowa River from October 1977 through October 1978 ranged from <0.5 ppb (detection limit) to 6 ppb, with an average concentration of 1.7 ppb (Veenstra and Schnoor, 1980). Bromoform was detected in 35.3% of water samples from 17 stations in the lower Niagara River in 1981 at concentrations ranging from trace to 6 ppt (Kaiser et al., 1983). Also, bromoform was detected in 12.2% of water samples from 82 stations in Lake Ontario in 1981 at concentrations ranging from trace to 7 ppt (Kaiser et al., 1983), and in 7% of 30 water samples collected in the Delaware River basin in February, 1976 (DeWalle and Chian, 1978). A North Sea survey that included 108 samples of water from 9 locations collected on 6 cruises during 1983 and 1984 found bromoform at concentrations ranging from <5 ppt (detection limit) to 264 ppt, with average and median concentrations of 23 and 7 ppt, respectively (van de Meent et al., 1986). Water samples collected in 1985 from

the North and South Atlantic Ocean contained bromoform at concentrations of 0.8 and >6 ppt, respectively (Class et al., 1986).

The U.S. EPA STORET Data Base (U.S. EPA, 1988) indicates that bromoform was found in samples of sediment (44 total samples) at a concentration range of 0.10-0.025 ppm (wet weight) and an average concentration of 0.014 ppm.

Bromoform was detected in the secondary effluent from one of nine publicly owned treatment works in Illinois in 1980 (Ellis et al., 1982).

Rainwater from three of four storms in a semi-rural area of Portland, OR, during March-April 1982 contained bromoform at concentrations ranging from 0.26-0.50 ppt, with an average concentration of 0.3 ppt (Pankow et al., 1984). Rainwater from five storms in a residential area of Southeast Portland, OR, during October-December 1982 contained bromoform at concentrations ranging from 0.18-1.5 ppt, with an average concentration of 0.88 ppt (Pankow et al., 1984). Rainwater samples from Southern Germany collected in 1985 contained bromoform at a concentration of 5 ppt (Class et al., 1986).

3.2. FOOD

Pertinent data regarding exposure to bromoform by ingestion of contaminated food were not located in the available literature cited in Appendix A. Gschwend et al. (1985) reported that bromoform appears to be a natural product in the marine environment, and that the compound was quantified in several species of algae including the brown algae, Ascophyllum nodosum (150-12,500 ppb dry weight, 4500 ppb average), and Fucus vesiculosis (140-4700 ppb, 2200 ppb average); the green algae, Entormorpha linza (not detected-850 ppb) and Ulva lacta (1700-14,000 ppb); and the red algae, Gigartina crispus (not detected-2100 ppb). Bromoform is produced by a red seaweed of the genus Asparagopsis at a concentration of 1% of the total plant composition (dry weight) (Callahan et al., 1979).

3.3. INHALATION

Ambient air samples at four selected sites in the California South Coast air basin were surveyed for the presence of halogenated hydrocarbons between November 1982 and December 1983 (Shikiya et al., 1984). The sites were located in downtown Los Angeles (DOLA) near three freeways, 15 km east of DOLA downwind of urban areas and light industry, 25 km south of DOLA downwind of heavy industry, and 75 km east of DOLA downwind of urban area. Thirty-one percent of the samples detected bromoform above its quantitation limit (0.01 ppb). Peaks in the concentration of bromoform were observed at the various sites in May and June, with the DOLA site registering the highest composite mean (0.04 ppb) and highest monthly mean (0.31 ppb) in June 1983 (Shikiya et al., 1984).

Bromoform was detected in the ambient air at the following U.S. locations [location and year, number of samples/percent of samples positive, range and mean (ng/m^3)]: El Dorado, AR, 1976-1977, 46/76%, ND-2.7, 0.81; Lake Charles, LA, 1978, 4/100%, 6.6-71, 50; Magnolia, AR, 1977, 28/89.3%, ND-8.3, 1.5 (Brodzinsky and Singh, 1982).

Bromoform was found in 100% of 34 samples of Arctic air from 8 sites near Alaska, Greenland, Norway and the North Pole; the samples were collected during March and April 1983 (Berg et al., 1984). The concentrations of the compound ranged from 2-46 ppt, with an average of 15 ppt.

3.4. DERMAL

Occupational exposure standards warn of possible significant skin absorption for bromoform under industrial exposure conditions (OSHA, 1976); however, no evidence in the available literature cited in Appendix A indicates that dermal exposure contributes significantly to the total dose of tribromomethane for the general public (U.S. EPA, 1980a).

Beech et al. (1980) monitored tribromomethane levels in swimming pools in the Miami area. Tribromomethane concentrations in 101 city and beachfront freshwater pools averaged ≤0.002 mg/ℓ, which is consistent with levels monitored in drinking waters; however, bromoform concentrations monitored in 18 beachfront saline pools averaged 0.651 mg/ℓ, an increase of >300-fold. The increase was attributed to the bromide ion concentrations in the salt water. Beech et al. (1980) suggested that the absorption of trihalomethanes through the skin in pools should be studied further.

3.5. SUMMARY

Exposure of the general population to bromoform is most likely to occur from ingestion of contaminated drinking water and inhalation of contaminated ambient air. Minor dermal exposure may occur in swimming pools, especially beachfront pools that use salt water. Occupational exposure standards warn of possible significant skin absorption for tribromomethane under industrial exposure conditions (OSHA, 1976), but no evidence in the available literature cited in Appendix A indicates that dermal exposure contributes significantly to the total dose of tribromomethane for the general public (U.S. EPA, 1980a). Bromoform has been found in samples of drinking water, groundwater, surface water, effluent from publicly-owned treatment works, sediment, marine algae and ambient air. The U.S. EPA STORET Data Base (U.S. EPA, 1988) indicates that bromoform was found in samples of sediment (44 total samples) at a concentration range of 0.10-0.025 ppm (wet weight) and an average concentration of 0.014 ppm. Bromoform has been found in several species of algae, but no information regarding its presence in foods was found in the available literature cited in Appendix A.

4. ENVIRONMENTAL TOXICOLOGY

4.1. AQUATIC TOXICOLOGY

4.1.1. Acute Toxic Effects on Fauna. The 24-, 48-, 72- and 96-hour LC_{50}s (and 95% confidence limits) for bluegill sunfish, Lepomis macrochirus, exposed to bromoform were 33.2 (27.4-42.2), 33.2 (27.4-42.2), 30.5 (25.0-37.9) and 29.3 ppm (24.0-36.2), respectively (U.S. EPA, 1978). The 96-hour no effect concentration was reported as 13.0 ppm (U.S. EPA, 1978).

Gibson et al. (1979a,b, 1981) determined the acute toxicity of bromoform to clams, Protothaca staminea and Mercenaria mercenaria, oysters, Crassostrea virginica, shrimp, Penaeus aztecus, and menhaden, Brevoortia tyrannus. Specimens of P. staminea were held in 30 ℓ glass aquaria with ~5 cm of coarse sand and flowing seawater for 4 days before the initiation of testing. Bromoform was introduced into the exposure tanks by bubbling bromoform-saturated air through the tanks. Bromoform-contaminated air flows were adjusted to maintain target concentrations. Salinity and temperature were not measured, but seasonally range from 29-31 ppt and 7-13°C, respectively, for the period of testing. Shrimp and menhaden held in circular outdoor holding tanks with a continuous supply of sand and activated charcoal-filtered seawater were fed Purina trout chow on a daily basis. M. mercenaria and oysters were held in fiberglass water tables supplied with unfiltered seawater. Food other than that present in the seawater was not provided. Clams and shrimp were tested separately, while oysters and menhaden were exposed in a common chamber. The 96-hour LC_{50}s (and 95% confidence intervals) for shrimp and menhaden were 26 (20-33) and 12 mg/ℓ (9-15), respectively. Inadequate levels of mortality among molluscs exposed to the highest concentrations of bromoform prevented calculation of LC_{50}s for these species, which the investigators estimated would be >30-40 mg/ℓ.

Buccafusco et al. (1981) exposed bluegill sunfish, L. macrochirus, to bromoform in well water at a test temperature of 21-23°C under static conditions. They reported nominal 24- and 96-hour LC_{50}s of 33 and 29 mg/ℓ, respectively. Confidence intervals (95%) were reported for the 96-hour LC_{50} only (24-36 mg/ℓ).

Heitmuller et al. (1981) exposed sheepshead minnows, Cyprinidon variegatus, to bromoform in filtered natural seawater in static tests for 96 hours. Test solutions were not aerated during the study, which was conducted at a temperature of 25-31°C. These investigators reported nominal 24- and 48-hour LC_{50} values (and 95% confidence limits) of 19 ppm (16-23) and 72- and 96-hour LC_{50} values (and 95% confidence limits) of 18 ppm (15-21), respectively. The investigators also reported a NOEC of 2.9 ppm. U.S. EPA (1978) reported a NOEC for sheepshead minnow exposed to bromoform of 4.83 ppm and an MATC of >4.83 to <8.5 ppm.

Ward et al. (1981) also assessed the acute toxicity of bromoform to sheepshead minnows, C. variegatus. Juvenile fish were exposed to bromoform diluted with natural seawater in an intermittent-flow system delivering 1 ℓ/cycle at a rate of 4-7 cycles/hour. Salinity of seawater during the 96-hour study was 28/mℓ, with a mean temperature of 30°C. The investigators reported a 96-hour LC_{50} (and 95% confidence limits) of 7.1 mg/ℓ (4.6-11).

Mattice et al. (1981) and Trabalka et al. (1979) assessed the acute toxicity of bromoform to common carp, Cyprinus carpio, embryos in a static renewal study. Recently fertilized eggs (100-300 per treatment) were exposed to bromoform in 300 µℓ glass dishes at a test temperature of 26°C until hatching was complete (within 3-5 days). Test solutions were renewed 45 minutes after eggs were first placed in test solutions and every 8 hours

thereafter. The nominal LC_{50} (and 95% confidence limits) for eggs exposed to bromoform from the end of water hardening of the egg to hatching was 76 mg/ℓ (74-79). The investigators also calculated a weighted LC_{50} to take into account degradation of bromoform between changes of toxicant solution. The weighted LC_{50} was calculated to be 52 mg/ℓ, with 95% confidence limits ranging from 50-54 mg/ℓ. The calculated half-life for bromoform under the conditions of the study was 6.9 hours.

The 24- and 48-hour LC_{50}s (and 95% confidence limits) for the freshwater cladoceran, Daphnia magna, exposed to bromoform were 55.6 (43.9-67.6) and 46.5 ppm (42.3-51.4), respectively (U.S. EPA, 1978). The 48-hour NOEC was reported as <7.8 ppm (U.S. EPA, 1978).

The 24-, 48-, 72- and 96-hour LC_{50}s (and 95% confidence limits) for the saltwater crustacean, Mysidopsis bahia, exposed to bromoform were 76.3 (48.6-134), 60.1 (37.6-100), 60.1 (37.6-100) and 24.4 ppm (16.9-32.6), respectively (U.S. EPA, 1978). The 96-hour NOEC was reported as 8.67 ppm (U.S. EPA, 1978).

Trabalka and Burch (1978) assessed the toxicity of bromoform to the cladoceran, Daphnia pulex. Tests were conducted at 20±1°C in 80 mℓ of test solution with 2 daphnids/replicate and 10 replicates/concentration. Daphnids were fed trout chow twice weekly. The investigators reported a 96-hour LC_{50} of 44 mg/ℓ for D. pulex exposed to bromoform.

Stewart et al. (1979) assessed the toxicity of bromoform to larvae of the oyster, C. virginica. Tests were conducted at 26-29°C for 48 hours in aluminum foil-capped 1 ℓ glass beakers containing 1 ℓ of test solution. Each beaker was inoculated with ~1500 freshly spawned and fertilized oyster eggs to begin the test. Mortality among exposed larvae was determined by screening larvae from test solutions, resuspending in 250 mℓ of seawater and examining subsamples of this solution in a Sedgewick-Rafter Cell.

Studies were repeated 5 times at 1-week intervals. The investigators reported >90, ~83, ~75, 50 and ~42% survival among larvae exposed to bromoform at initial concentrations of 0.0, 0.05, 0.1, 1.0 and 10.0 mg/ℓ, respectively, for the 48-hour exposure period. Bromoform levels fell to 30% of their initial concentration by the end of the study.

LeBlanc (1980) exposed the water flea, D. magna, to bromoform in deionized reconstituted well water at 22±1°C with a mean hardness of 173±13 mg/ℓ as $CaCO_3$. Test concentrations were not measured during the 48-hour static test. Test vessels (250 mℓ beakers) were covered with plastic wrap secured with an elastic band. The reported 24- and 48-hour LC_{50}s and 95% confidence limits were 56 (44-68) and 46 mg/ℓ (42-51), respectively. The NOEC was <7.8 mg/ℓ.

Kerster and Schaeffer (1983) assessed the teratogenic effects of bromoform in brine shrimp, Artemia salina. Evidence for teratogenesis in this assay was derived from disturbances in elongation development of stage I to stage III nauplii during the first 24-48 hours after hatching at 25°C. Inhibition of elongation by ≥20% in bromoform-exposed nauplii compared with elongation of control nauplii was considered indicative of teratogenesis. The investigators reported that bromoform was teratogenic to brine shrimp nauplii at concentrations of 0.25-25 ppm, but that the assay was not very sensitive with high animal-to-animal variability.

Richie et al. (1984) determined the toxicity of bromoform to larval mosquitoes, Aedes aegypti. Exposure of larvae to bromoform was conducted in 14.5x1.3-cm screw cap culture tubes at 29°C, with a single larvae in 5 mℓ of solution/tube with 10 tubes/treatment. Test larvae were newly-hatched, first instar stages. The investigators reported 0.5, 1.0 and 24-hour LC_{50}s of 250, 80 and 75 ppm, respectively.

4.1.2. Chronic Effects on Fauna.

4.1.2.1. TOXICITY -- Maddock and Kelly (1980) examined the potential of an *in vitro* SCE assay in leukocytes from the marine oyster toadfish, *Opsanus tau*, as a mechanism to detect waterborn mutagens and carcinogens. Leukocytes were obtained from samples of whole blood collected from living fish. Cells were cultured in an appropriate medium for 72 hours at 25°C before the addition of bromoform dissolved in a balanced salt solution. Cultures were harvested 3-5 days after the introduction of bromoform. The investigators reported that exposure of dividing leukocytes to bromoform at 0.1 and 400 µg/mℓ did not result in an increased rate of SCE, and speculated that the genetic activity of bromoform may be detectable at higher concentrations or require metabolic activation in an *in vivo* assay.

Ward et al. (1981) assessed the chronic toxicity of bromoform to embryos and juveniles of sheepshead minnows, *C. variegatus*. Exposure of embryos continued until all had either hatched or died. Juveniles from hatched embryos were exposed to bromoform for 28 days. Embryos and juveniles were exposed to bromoform diluted with natural seawater in an intermittent-flow system delivering 1 ℓ per cycle at a rate of 4-7 cycles/hour. Juveniles were fed live brine shrimp nauplii daily. Toxicant concentrations were measured weekly. Test endpoints were percent hatching success and juvenile mortality. Salinity of seawater during the study ranged from 21-28/mℓ, with a mean temperature of 30°C. Mean bromoform concentrations were 52-89% of nominal concentrations, ranging from 1.6-15 mg/ℓ. The investigators reported that exposure to $\leq$15 mg/ℓ had no effect on hatching success or growth of surviving juveniles. Concentrations $\geq$8.5 mg/ℓ significantly increased mortality among juveniles, producing an estimated MATC of >4.8 to <8.5 mg/ℓ.

4.1.2.2. BIOACCUMULATION/BIOCONCENTRATION -- Anderson et al. (1979) and Gibson et al. (1979a,b,c, 1981) monitored the bioaccumulation and depuration of bromoform in clams, P. staminea and M. mercenaria, oysters, C. virginica, shrimp, P. aztecus, and menhaden, B. tyrannus. Holding and exposure regimens were identical to those described above for acute toxicity testing of bromoform with these species. P. staminea was tested separately from the other species, which were exposed in a common chamber at concentrations ranging from 1-20 mg/ℓ. Exposure concentrations for the other molluscs ranged from 0.03-0.99 mg/ℓ, and for menhaden and shrimp, 0.03-0.29 mg/ℓ. The investigators reported that the clams and oysters had tissue concentrations approximately equal to the water concentrations for the 28 days of the exposure phase. Menhaden and shrimp, however, concentrated bromoform 3- to 50-fold above the exposure concentration, although body burden levels tended to plateau at 0.4 µg/g tissue. Depuration of bromoform from tissues of exposed organisms was very rapid, with negligible levels present within 2 days of the cessation of exposure.

Scott et al. (1980) assessed the uptake of chlorination by-products in the American oyster, C. virginica, during short-term exposures. Oysters were acclimated to running seawater (25 ℓ/hour) for 15 days in experimental chambers before the introduction of chlorine-produced oxidants (free plus combined chlorine, bromine and other residual oxidants) at a concentration of 0.18 mg/ℓ for 96 hours. Bromoform concentrations ranged from 0.93-3.27 (mean = 2.03) µg/ℓ. Water temperature ranged from 23.3-25.5°C. Salinity ranged from 18.0-21.5 ppt. The investigators reported a 3-fold bioconcentration of bromoform in oyster tissues. Bromoform concentrations in oyster tissues after 0, 24, 48, 72 and 96 hours were 0, 0, 12, 6.5 and 6 µg/kg, respectively. Tissue bromoform concentrations

fell from 6 µg/kg to 0 µg/kg within 48 hours of the cessation of exposure to chlorine-produced oxidants. The authors noted that the uptake of bromoform by oysters could be seasonally dependent and based on physiological changes in the oysters.

Subsequently, Scott et al. (1982, 1983) exposed oysters, C. virginica, to chlorinated seawater for an extended duration. Tests were conducted in replicate tanks (110x63x28 cm), with 50 oysters each receiving 250 ℓ of unfiltered seawater/hour. Exposure concentration was 1.0 mg chlorine/ℓ as $Ca(OCl)_2$, producing mean bromoform concentrations of 28.3 and 21.9 µg/ℓ in replicate chambers. Water temperature ranged from 26.5-30.0°C and salinity ranged from 24-30 ppt. Measured levels of bromoform in oyster tissue on days 0, 4, 8, 16 and 32 were 0, 100, 20, 35 and 65 ng/g wet weight, respectively. Tissue levels of bromoform fell from ~65 ng/g wet weight to 0 ng/g wet weight within 4 days of the termination of exposure to chlorinated seawater.

Based on the regression equation, log BCF = 0.76 log K_{ow} - 0.23 (Lyman et al., 1982) and a log K_{ow} value for bromoform of 2.37 (see Section 1.2.), a BCF value of 37.3 is estimated for this compound. This value is in agreement with the experimentally-derived BCFs of 3- to 50-fold, demonstrating that bromoform does not bioaccumulate significantly in aquatic organisms.

4.1.3. Effects on Flora.

4.1.3.1. TOXICITY -- The 24-, 48- and 72-hour EC_{50}s (and 95% confidence limits) for cultures of the freshwater green alga, Selanastrum capricornutum, exposed to bromoform were 184 (21.3-51.1), 134 (82.6-250) and 121 ppm (86.4-169), respectively (U.S. EPA, 1978). Two 96-hour EC_{50}s (and 95% confidence limits) reported for this species were 112 (75.4-155) and 116 ppm (81.2-160) (U.S. EPA, 1978). The 96-hour NOEC was reported to be 28.9 ppm (U.S. EPA, 1978).

The 24-, 48- and 72-hour EC_{50}s (and 95% confidence limits) for cultures of the saltwater alga, Skeletonema costatum, exposed to bromoform were >28.9, 15.1 (12.0-18.1) and 13.5 ppm (7.54-30.3), respectively (U.S. EPA, 1978). Two 96-hour EC_{50}s (and 95% confidence limits) reported for this species were 12.3 (5.92-25.8) and 11.5 ppm (5.35-24.9) (U.S. EPA, 1978). The 96-hour NOEC was reported to be 1.73 ppm (U.S. EPA, 1978).

Erickson and Hawkins (1980) assessed the effects of bromoform on photosynthesis by estuarine phytoplankton. Taxonomic classes present during sampling included Chlorophyceae, Cyanophyceae, and Bacillariophyceae. Seawater was pumped to eight 37 ℓ aquaria located on an outdoor table at a rate of 40 ℓ/hour. Water temperature ranged from 19.5-21.5°C and salinity ranged from 20-24 g/ℓ. Exposure concentrations of bromoform ranged from 0.5-2.0 mg/ℓ. Photosynthesis was determined by ^{14}C uptake following exposure to bromoform for 24 hours. The investigators reported no statistically measurable effects on ^{14}C uptake by estuarine phytoplankton exposed to bromoform at the tested concentrations.

4.1.3.2. **BIOCONCENTRATION** -- Pertinent data regarding the bioconcentration potential of bromoform in aquatic flora were not located in the available literature cited in Appendix A.

4.1.4. Effects on Bacteria. Pertinent data regarding the effects of exposure of aquatic bacteria to bromoform were not located in the available literature cited in Appendix A.

4.2. TERRESTRIAL TOXICOLOGY

4.2.1. Effects on Fauna. Pertinent data regarding the effects of exposure of terrestrial fauna to bromoform were not located in the available literature cited in Appendix A.

4.2.2. Effects on Flora. Pertinent data regarding the effects of exposure of terrestrial flora to bromoform were not located in the available literature cited in Appendix A.

4.3. FIELD STUDIES

Pertinent data regarding the effects of bromoform on flora and fauna in the field were not located in the available literature cited in Appendix A.

4.4. SUMMARY

The acute toxicity of bromoform to freshwater fish was determined for bluegill sunfish and common carp. The 96-hour LC_{50}s for sunfish exposed to bromoform were 29.3 ppm (U.S. EPA, 1978) and 29 mg/ℓ (Buccafusco et al., 1981). The NOEC reported by U.S. EPA (1978) was 13 ppm. Mattice et al. (1981) and Trabalka et al. (1979) reported that the LC_{50} for common carp eggs exposed to bromoform was 52 mg/ℓ. The acute toxicity of bromoform to saltwater fish was determined for menhaden and sheepshead minnow. The 96-hour LC_{50} for menhaden exposed to bromoform was 12 mg/ℓ (Gibson et al., 1979a,b, 1981). The 96-hour LC_{50} for sheepshead minnow exposed to bromoform was 18 ppm in a static test (Heitmuller et al., 1981) and 7.1 mg/ℓ in a flowthrough test (Ward et al., 1981). Heitmuller et al. (1981) reported a NOEC of 2.9 ppm, while U.S. EPA (1978) reported a NOEC for sheepshead minnow exposed to bromoform of 4.83 ppm and a MATC of >4.83 to <8.5 ppm.

The acute toxicity of bromoform to molluscs was reported by Stewart et al. (1979) and Gibson et al. (1979a,b, 1981). Survival among larvae of the American oyster fell from >90 to ~42% at bromoform concentrations from 0-10 mg/ℓ. Inadequate levels of mortality among adult clams and oysters prevented calculation of LC_{50}s for these species.

U.S. EPA (1978) and LeBlanc (1980) reported 48-hour LC_{50}s for Daphnia magna of 46.5 ppm, with a NOEC of <7.8 ppm. The 96-hour LC_{50} for a related species, Daphnia pulex, was 44 mg/ℓ (Trabalka and Burch, 1978). Richie et al. (1984) reported a 24-hour LC_{50} of 75 ppm for larval mosquitoes exposed to bromoform.

The 96-hour LC_{50} for the saltwater crustacean, Mysidopsis bahia, was 24.4 ppm, while the NOEC was reported as 8.67 ppm (U.S. EPA, 1978). Gibson et al. (1979a,b, 1981) reported a 96-hour LC_{50} for shrimp of 26 mg/ℓ. Kerster and Schaeffer (1983) reported that bromoform was not teratogenic to brine shrimp nauplii at concentrations of 0.25-25 ppm.

Ward et al. (1981) reported that bromoform at concentrations of $\leq$15 mg/ℓ had no effect on hatching success or growth of surviving sheepshead minnow juveniles, while concentrations $\geq$8.5 mg/ℓ significantly increased mortality among juveniles, producing an estimated MATC of >4.8 to <8.5.

Anderson et al. (1979), Gibson et al. (1979a,b,c, 1981) and Scott et al. (1980, 1982, 1983) reported that bromoform was bioaccumulated 3- to 50-fold by clams, oysters, shrimp and fish, but that depuration was very rapid (<2-4 days). A BCF value calculated from the log K_{ow} for bromoform also indicates that bromoform does not bioaccumulate significantly.

U.S. EPA (1978) reported 96-hour EC_{50}s for cultures of the freshwater green alga, Selanastrum capricornutum, exposed to bromoform of 112 and 116 ppm, with a NOEC of 28.9 ppm. U.S. EPA (1978) also reported 96-hour EC_{50}s for cultures of the saltwater alga, Skeletonema costatum, exposed to bromoform of 12.3 and 11.5 ppm, with a NOEC of 1.73 ppm.

5. PHARMACOKINETICS

5.1. ABSORPTION

Absorption of bromoform occurs from the respiratory tract during inhalation, through the skin and from the gastrointestinal tract (von Oettingen, 1955). Quantitative information was not available on the rate or extent of dermal or inhalation absorption. Sax (1984), however, reported that dogs exposed to bromoform at a concentration of 29,000 ppm experienced deep narcosis after an 8-minute exposure, deep narcosis and recovery 1 day later after a 30-minute exposure and death following a 1-hour exposure. Merzbach (1928) also reported that a dog exposed to bromoform at a level of 56,000 ppm became deeply anesthetized after 20 minutes and died after 1 hour. Dykan (1962, 1964) described toxic effects in rats and rabbits caused by exposure to bromoform fumes. Collectively, these data suggest that substantial and rapid absorption occurs from the respiratory tracts of several species.

Gastrointestinal absorption in mice was determined by Mink et al. (1986). Commercially synthesized $^{14}CHBr_3$ was diluted in corn oil and administered by gavage in single doses of 100 mg/kg for rats and 150 mg/kg for mice. Test animals (adult male Sprague-Dawley rats and adult male B6C3F1 mice) were fasted 16 hours overnight before treatment. Recovery of the labeled carbon was evaluated after administration of a single dose of the test substance. At 8 hours after treatment, 75.5% of the total ^{14}C administered was recovered from the rats: 66.9% expired as parent compound, 4.3% as carbon dioxide, 2.2% in urine and 2.1% in selected organs previously determined to be the only ones with levels of radiation above background.

From the mice, 62.2% was recovered: 5.7% expired as parent compound, 39.7% as carbon dioxide, 4.6% in urine and 12.2% in selected organs. Fecal excretion of bromoform or its metabolites was not estimated. Graphs suggested that most of the expiration of radioactivity had occurred by ~5 hours postdosing for mice and 2 hours postdosing for rats. These data suggest that gastrointestinal absorption is rapid, and that total gastrointestinal absorption is at least 75.5% of a single gavage dose in rats and 62.2% in mice.

5.2. DISTRIBUTION

Parra et al. (1986) reported that bromoform distributed preferentially to adipose tissue of 24-hour fasted adult male Sprague-Dawley rats given a single gavage dose of 12 mg/kg in distilled water. At 15 minutes after treatment, levels in fat (~8800 ng/g fresh tissue) were ~1 order of magnitude greater than those in blood (~820 ng/g). Somewhat lower levels were found in kidney (740 ng/g), brain (~570 ng/g) and liver (~30 ng/g). Levels in the liver declined to below detection limit by 1 hour, presumably because metabolism of bromoform occurred rapidly in this organ. Levels in the remaining tissues other than fat declined to below detection by 4 hours. At 4 hours, levels in fat had declined to 1570 ng/kg. The investigators concluded that distribution and elimination of bromoform occurred rapidly. Mink et al., (1986) evaluated distribution of radiolabeled bromoform in rats and mice. At an unspecified time after intragastric intubation of $^{14}CHBr_3$ in rats and mice (see Section 5.1.), ~2% of the total radioactivity administered was found in the urinary bladder, brain, kidneys, liver, lungs, skeletal muscle, pancreas, stomach (without contents) and thymus. In addition, ~10% was found in the blood of the mice. The investigators reported that these organs were the only ones that contained a significant amount of radioactivity above the background level. Organs with

the highest residual radioactivity levels were the stomach without contents, nonperfused liver, and kidneys for both rats and mice. Leuze (1922), however, reported that after inhalation exposure, higher concentrations of bromoform were found in the brain than in the blood or liver.

5.3. METABOLISM

Intraperitoneal or inhalation administration of trihalomethanes to rats resulted in elevated blood CO and carboxyhemoglobin levels (Anders et al., 1978; Fodor and Roscovanu, 1976) and lowered liver GSH levels (Pohl et al., 1980a). Moody and Smuckler (1986), however, detected a significant increase in GSH levels in rats administered bromoform by gavage at a level of 1000 mg/kg. Bromoform is metabolized to CO by a cytochrome P450-dependent mixed-function oxidase system in rat liver microsomal fraction (Ahmed et al., 1977; Stevens and Anders, 1979; Ahmed et al., 1980). This metabolism requires NADPH, molecular oxygen and a sulfhydral compound (e.g., GSH) for maximum activity (Ahmed et al., 1977; Stevens and Anders, 1979). This GSH-dependent CO production is part of the detoxification pathway for bromoform and haloforms in general (Stevens and Anders, 1981). The fate of the carbon in bromoform and the molecular oxygen during metabolism was studied in vitro by Stevens and Anders (1979). $^{13}CHBr_3$ and $^{12}CHBr_3$ incubated in the presence of $^{18}O_2$ produced ^{13}CO and $C_{18}O$, respectively. A primary isotope effect was observed when C^2HBr_3 served as the substrate.

The overall metabolic pathway (Figure 5-1) includes the role of dibromocarbonyl, proposed as a toxic intermediate in the metabolism of bromoform, in the formation of OZT, CO and CO_2 (NTP, 1988). Dibromocarbonyl is an intermediate in the production of CO from bromoform as shown by the detection of OZT when bromoform was incubated with cysteine. The source of the

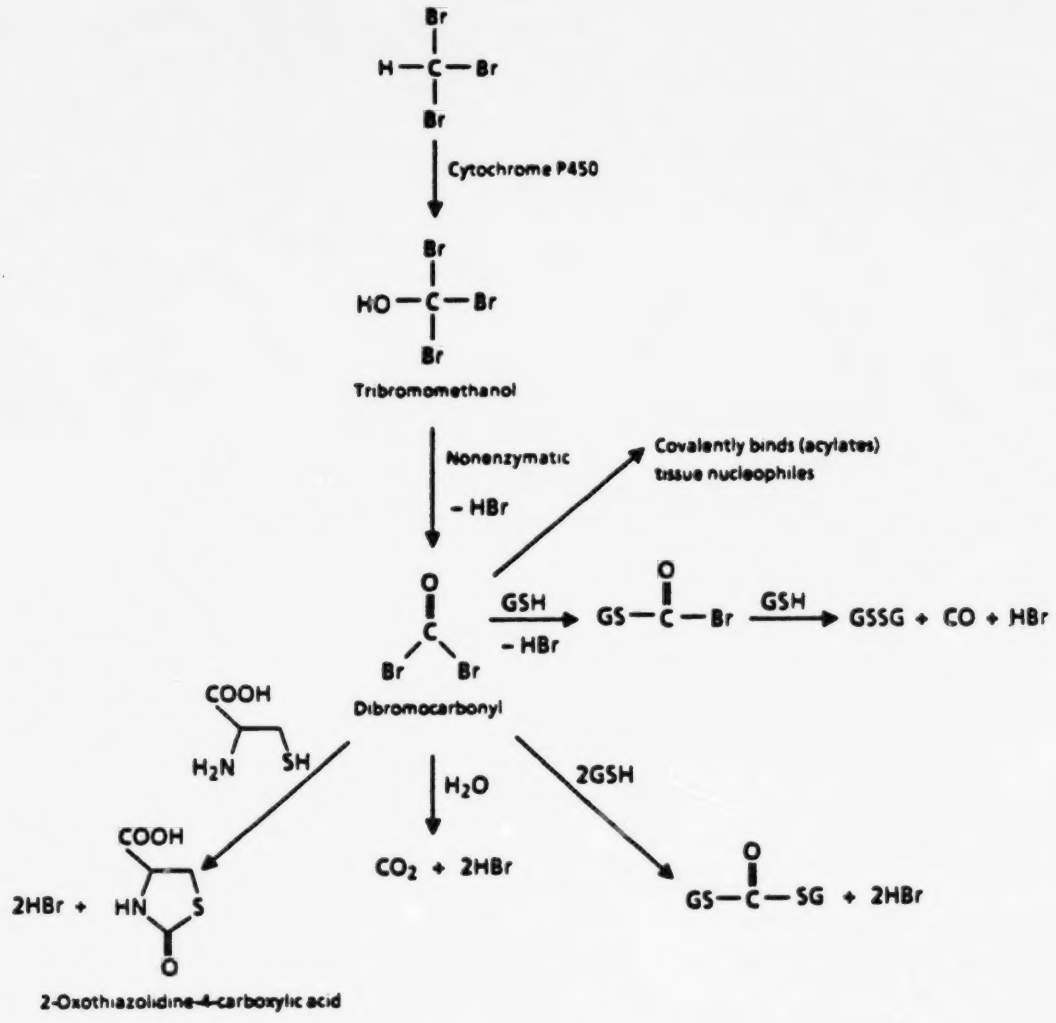

FIGURE 5-1

Proposed Metabolic Pathway for Bromoform

Source: NTP, 1988

carbonyl carbon was shown to be bromoform, because [^{13}C]OZT was formed when ^{13}C bromoform was the substrate. The oxidized form of GSH (GSSG) is apparently produced when COX_2, formed during oxidative metabolism of halocarbons, react with GSH (Pohl et al., 1980a). GSH becomes oxidized to GSSG and CO is formed from dibromocarbonyl in a ratio of 2:1:1 GSH:GSSG:CO (Stevens and Anders, 1979).

The toxicity of trihalomethane metabolites may be related to their reducing mechanisms (Tomasi et al., 1985; Wolf et al., 1977). Free radical intermediates were found during aerobic and anaerobic incubation of bromoform with isolated rat hepatocytes (Albano et al., 1985; Tomasi et al., 1985). Poyer et al. (1986) also detected a dibromomethyl radical ($\cdot CHBr_2$) in rat liver lipid extracts 2 hours after ingestion of bromoform at a level of 1.3 mmol/kg (~330 mg/kg) body weight. The bromoform was administered along with phenyl-t-butyl nitrone (a spin trapping agent) in a corn oil-phosphate buffer mixture by oral gavage. This radical was also detected in in vitro incubation of bromoform with liver microsomes from the mouse, chicken and turkey. Wolf et al. (1977) suggested that the radical may lead to lipid peroxidation and destruction of cell membranes, and NTP (1988) suggested that covalent binding of cellular macromolecules by dibromocarbonyl (the intermediate) may be the cause of liver toxicity.

Many factors may inhibit or enhance the rate of bromoform metabolism in vitro and in vivo. The rate of conversion of bromoform to CO was inhibited in vivo or in vitro by pretreating rats with cobaltous chloride (Ahmed et al., 1977), SKF 525-A (a hepatic microsomal cytochrome P450 inhibitor) (Ahmed et al., 1977; Anders et al., 1978), diethylmaleate (also an inhibitor of the cytochrome P450-dependent oxidation of some xenobiotics) (Stevens and Anders, 1981) and CO (Buther et al., 1986). The in vivo and in vitro rate

of conversion was increased by pretreating rats with phenobarbital (Ahmed et al., 1977; Wolf et al., 1977; Anders et al., 1978) or 3-methylcholanthrene (Ahmed et al., 1977). Pohl et al. (1980b) reported that phenobarbital pretreatment of rats induced liver microsomal formation of $COBr_2$ from .omoform.

Diethylmaleate pretreatment of male Sprague-Dawley rats 30 minutes before intraperitoneal injection of [^{2}H]bromoform (deuterium-substituted) also lessened the effect of deuterium substitution on the metabolism of bromoform to CO (Stevens and Anders, 1981). There was no significant difference between the blood CO concentrations produced by the deuterium substituted form of bromoform and the [^{1}H]bromoform in diethylmaleate pretreated rats, whereas Anders et al. (1978) detected lower blood CO levels in nonpretreated rats administered ^{2}H-bromoform (deuterium-substituted) compared with those administered ^{1}H-bromoform.

Pohl et al. (1980b) also determined that deuterium-labeled bromoform is less hepatotoxic than $CHBr_3$. The C-H cleavage is the rate limiting step in the biotransformation of bromoform to hepatotoxic metabolites (NTP, 1988; Anders et al., 1978). Deuterium (which presumably forms a stronger C-H bond) has been shown to decrease the rate of bromoform metabolism; homolytic scission of the C-H bond is critical for aerobic haloform metabolism. In a reductive environment, however, deuterium substitution does not significantly affect the rate of free radical formation. This suggests that there is an electron transfer directly from the cytochrome to the halocompound (bromoform), with the subsequent formation of a halide ion and the free radical (Tomasi et al., 1985), a mechanism not dependent on lysis of the C-H bond.

Excretion data (Section 5.4.) suggest substantial quantitative differences between species in the metabolism of bromoform.

5.4. EXCRETION

Mink et al. (1986) studied the excretion of radiolabeled bromoform in orally treated rats and mice (see Section 5.1.). The urine of both the mice and rats contained <5% of the total radiolabel 8 hours after gavage administration and <10% after 36-48 hours. Most of the bromoform was eliminated through the lungs in the expired air within 8 hours postdosing for both the rats and the mice. The mice eliminated 39.68% of the total ^{14}C-bromoform as $^{14}CO_2$ and 5.70% as the unmetabolized parent compound. The rats, however, eliminated 4.3% as $^{14}CO_2$ and 66.9% as the parent compound. These data suggest that mice metabolize bromoform more extensively than do rats. The half-lives of bromoform were 8 hours in mice and 0.8 hours in rats. Lucas (1928) also evaluated excretion of bromoform and its metabolites in the urine. Several male rabbits were injected with a 50:50 bromoform-olive oil mixture per rectum and were catheterized for several days to collect urine samples. The bromoform was recovered as inorganic bromide in the urine in amounts ranging from 0.3-1.2%.

5.5. SUMMARY

Bromoform is absorbed from the respiratory tract, skin and gastrointestinal tract (von Oettingen, 1955), apparently quite readily from the respiratory and gastrointestinal tracts. Once absorbed, bromoform and its metabolites are distributed rapidly, with highest levels located in adipose tissue and blood (Parra et al., 1986). Substantial levels are also found in several other organs including the brain. Elimination occurs rapidly from all tissues including fat (Parra et al., 1986). Metabolism of bromoform occurs predominantly in the liver by a cytochrome P450 oxidase system to CO

and CO_2 (Ahmed et al., 1977, 1980; Stevens and Anders, 1979). Dibromocarbonyl is a likely toxic intermediate in this pathway (NTP, 1988). Mice appear to metabolize bromoform by this pathway more completely than do rats (Mink et al., 1986). Bromoform metabolism depletes liver GSH (Pohl et al., 1980a) because this system is stimulated by sulfhydral compounds (e.g., GSH) (Stevens and Anders, 1979; Ahmed et al., 1980). Bromoform also appears to be metabolized through a reductive pathway that produces free radical intermediates. Excretion of bromoform and its metabolites occurs to a small extent through the urine and to a much larger extent through the lungs in mice, rats (Mink et al., 1986) and rabbits (Lucas, 1928).

6. EFFECTS

6.1. SYSTEMIC TOXICITY

6.1.1. Inhalation Exposure.

6.1.1.1. SUBCHRONIC -- Dykan (1962) administered bromoform to rats at a level of 0.25 mg/ℓ (250 mg/m³) air, 4 hours/day for 2 months. Disorders were observed in the glycogenesis and protein prothrombin functions of the liver and the filtration capacity of the kidneys. Further information was not available in the abstract of this study.

6.1.1.2. CHRONIC -- Dykan (1964) evaluated the effects of chronic intoxication (details of administration not available from the abstract) of bromoform on rats and determined that the threshhold concentration was 0.05 mg/ℓ (50 mg/m³). Bromoform-containing metabolites were produced and slowly excreted from the animal. Dykan (1964) also stated that workers in bromoform production exhibited changes in the central nervous system and liver.

6.1.2. Oral Exposure.

6.1.2.1. SUBCHRONIC -- In a study sponsored by the NTP (1988), bromoform (95-97% pure) was administered in corn oil by gavage to groups of 10 male and 10 female F344/N rats and equal numbers of B6C3F1 mice 5 days/week for 13 weeks. The rats received bromoform at doses of 0 (vehicle control), 12, 25, 50, 100 or 200 mg/kg body weight and the mice received doses of 0 (vehicle control), 25, 50, 100, 200 or 400 mg/kg. Animals were observed daily and killed when moribund. Necropsy was performed on all animals except those severely autolyzed or cannibalized.

Clinical observation of the rats revealed no mortalities and no significant difference between final mean body weights of dosed and vehicle control rats. All male rats receiving 100 or 200 mg/kg and all females receiving

200 mg/kg were lethargic. Also, all males in the highest dose group had diarrhea. Histopathological evaluation of rats revealed hepatocellular vacuolization in males in 10/10 rats receiving 200 mg/kg, 8/10 receiving 100 mg/kg, 8/10 receiving 50 mg/kg, 5/10 receiving 25 mg/kg, 6/10 receiving 12 mg/kg and 3/10 in the vehicle control group. The incidence of hypatocellular vacuolization reached statistical significance at 50 mg/kg (8/10; p=0.03 Fisher Exact test computed at SRC). Vacuoles were more numerous in hepatocytes from rats in the highest dose group. Lesions were not observed in female rats.

Clinical observation revealed mortality in one female mouse that received 100 mg/kg of bromoform; cause of death was not reported. Males in the highest dose group had final mean body weights 8% lower than those of vehicle controls. Histopathological evaluation revealed dose-related cytoplasmic vacuolization of hepatocytes in the livers of 8/10 males in the 400 mg/kg dose group and 5/10 males in the 200 mg/kg dose group. The incidence in the control group was not reported. Lesions were not observed in female mice.

The RES was evaluated in 7-day-old male and female ICR mice administered bromoform by oral gavage for 90 days at dose levels ranging from 0.2-125 mg/kg (Munson et al., 1977). Blood clearance of I^{125}-labeled Listeria monocytogenes was decreased by 23% in males receiving the lowest dose of bromoform. The accumulation of L. monocytogenes was measured in the liver by determining specific activity. A dose-related depression in specific activity was observed in females and males that reached 43 and 28%, respectively, at 125 mg/kg. The decrease in blood clearance and specific activity indicated that there was a reduced uptake and disposal of phagocytic cells required for the removal of the L. monocytogenes pathogen. Munson et al.

(1977) concluded that there was a slight alteration in RES function after administration of bromoform. Munson et al. (1978) also reported a dose-dependent suppression in hepatic phagocytosis in female and male mice administered 0.3, 12.5 or 125 mg/kg/day. The level at which significant suppression first occurred is difficult to assess.

Balster and Borzelleca (1982) evaluated the behavioral toxicity of bromoform following oral gavage in a suspension using a vehicle of 1:8 Emulphor:water. Groups of 6-8 adult male ICR mice were administered bromoform at levels of 0.9 or 9.2 mg/kg/day for 90 days. There was no effect on bar clinging, exploratory behavior or motor coordination. Mice were also administered bromoform at a level of 100 or 400 mg/kg/day for 60 days or at a level of 100 mg/kg/day for 30 days. Operant behavior (response and reinforcement rates were decreased) was clearly impaired at both of the dose levels given for 60 days. Some tolerance developed to the initial operant behavior effects seen in this study. No effect on passive-avoidance learning was observed in the 30-day experiment.

Chu et al. (1982a) evaluated the reversibility of toxicological changes produced by some trihalomethanes. Groups of 20 male and 20 female weanling Sprague-Dawley rats were administered bromoform and Emulphor in their drinking water for 90 days at a level of 0 (tap water control), 0 (vehicle control), 5, 50, 500 or 2500 ppm. Drinking water intake decreased in a concentration-related manner. Based on water ingestion, the investigators estimated dosage at 0, 0.11-0.17, 1.2-1.5, 8.9-14 and 29-55 mg/rat/day. After 90 days, 10 rats from each group were killed and the remaining rats received plain tap water for another 90 days.

Mortality was observed in one male rat in the highest dose group, two females in the 500 ppm group and one female in the 5 ppm group. In the

groups allowed to recover, mortality was observed in one female in each group that had received 50 ppm, 500 ppm and 2500 ppm bromoform. Emaciation and weight loss were observed before death; microscopic examination suggested starvation as the cause of death.

According to Chu et al. (1982a), there was no significant effect on body weight changes during treatment or after the 90-day recovery period for either sex. Male rats receiving bromoform at 2500 ppm experienced suppressed food consumption, but this effect was not apparent after the 90-day recovery period. Other effects reported in both sexes at 2500 ppm were significantly decreased serum LDH activities, noted during both the exposure and recovery periods, and significantly decreased lymphocyte counts observed only during the recovery period. The biological significance of these observations is unclear. Mild histopathologic lesions were observed in the livers and thyroids of both control and exposed rats. Although it appeared that the number of rats bearing lesions was greater at 2500 ppm, the incidence was quite variable and not statistically significant. Significantly greater severity was observed in the liver lesions in males at 2500 ppm and in females at $\geq$500 ppm after exposure. There was no significant difference in the severity of these lesions after the recovery period.

Borzelleca (1983) studied the effects of bromoform administered in the drinking water on male and female CD-1 mice (group sizes not reported). Systemic toxicological parameters examined included hematology, numerous clinical chemistries, immunology, extensive behavior evaluation, neurochemical status and organ weights. Dosages ingested by adult male mice were estimated by the investigators at 0.2, 125 and 250 mg/kg/day for 90 days. There were no significant findings at any of these levels. Dosage and response data on female mice were not reported.

Chu et al. (1982b) evaluated the toxicity of bromoform (96% pure) in groups of 10 weanling male Sprague-Dawley rats administered the test substance with 1% Emulphor (a surfactant) in drinking water at levels of 0 (tap water), 0 (vehicle control), 5, 50 or 500 ppm (w/v) for 28 days. Dosages were estimated by the investigators at 0, 0, 0.13, 1.5 and 14 mg/rat/day. There were no treatment-related mortalities and no effects on the growth rate and food intake at any level. Necropsy evaluation revealed a slight increase in relative kidney weight in the 500 ppm group. No changes were observed in serum biochemical parameters (sodium, potassium, phosphate, total bilirubin, alkaline phosphatase, GOT, total protein, calcium, cholesterol, glucose, uric acid, LDH and SDH levels), hepatic microsomal enzyme activities and histological appearance of >25 major organs and tissues.

In a test of the effect of haloalkanes on humoral and cell-mediated immunity, Schuller et al. (1978) administered bromoform by gavage for 90 days (schedule not reported) to 7-day-old male and female ICR mice at levels of 0.2, 12.5 or 125 mg/kg. Bromoform did not appear to affect delayed hypersensitivity, humoral immune response, liver function, kidney function or hematology in the mice.

6.1.2.2. CHRONIC -- In a chronic oral toxicity study sponsored by NTP (1988), groups of 50 male and 50 female F344/N rats and 50 female B6C3F1 mice were administered bromoform in corn oil by gavage at levels of 0 (vehicle control), 100 or 200 mg/kg, 5 days/week for 103 weeks. Groups of 50 male B6C3F1 mice were similarily administered bromoform at levels of 0 (vehicle control), 50 or 100 mg/kg.

Compound-related mortality was observed only in the male rats receiving 200 mg/kg/day. Lethargy was observed in treated male and female rats, and

aggressiveness was also observed in treated male rats. Mean body weights of low- and high-dose males and high-dose female rats were substantially lower than those of vehicle controls by the end of the study (between 5 and 14% lower, 12 and 28% lower and 10 and 25% lower, respectively). Histopathological examination revealed an increased incidence of chemical-related, nonneoplastic lesions in the livers of treated rats. Dosed female rats displayed fatty liver changes, increased mixed cell foci, decreased basophilic foci and decreased necrosis of the liver when compared with control animals. Chemical-related effects in dosed male rats included fatty change, chronic inflammation and necrosis of the liver, and an increased incidence of gastric ulcers and chronic inflammation of the lungs.

There was no significant difference in mean body weights of treated male mice; however, weights of dosed female mice were 5-16% lower than those of vehicle controls. Histopathological examination revealed hyperplasia of the glandular stomach in treated males, cytoplasmic vacuolization of hepatocytes in treated females and thyroid follicular cell hyperplasia in high-dose females.

6.1.3. Other Relevant Information. Table 6-1 summarizes LD_{50} and LC_{50} data. Oral LD_{50} values for both rats and mice ranged from 1147-2500 mg/kg; there was no particularily sensitive species or sex. Intraperitoneal LD_{50} values ranged from 414 µℓ/kg (1196 mg/kg) for male rats (comparable with oral data) to 9274 mg/kg for unspecified mammals. According to Sax (1984), the inhalation LC_{50} value is 12,100 mg/m³ for mammals (length of time not stated).

Results of acute oral administration of bromoform to rats include: ataxia and lethargy (Chu et al., 1980; NTP, 1988); piloerection, flaccid muscle tone and hypothermia (Chu et al., 1980); altered hematological

TABLE 6-1

LD_{50} and LC_{50} Values for Bromoform

Species	Sex	Dose or Concentration (Vehicle)	Value	Reference
ICR Swiss mice/ CD-1 mice	M	1400 mg/kg (Emulphor: alcohol:saline)	oral LD_{50}	Bowman et al., 1978; Borzelleca, 1983
ICR Swiss mice/ CD-1 mice	F	1550 mg/kg (Emulphor: alcohol:saline)	oral LD_{50}	Bowman et al., 1978; Borzelleca, 1983
Rats	M	2500 mg/kg (corn oil)	oral LD_{50}	Torkelson and Rowe, 1981
Sprague-Dawley rats	M	1388 mg/kg (Emulphor: water)	oral LD_{50}	Chu et al., 1982b
Sprague-Dawley rats	F	1147 mg/kg (Emulphor: water)	oral LD_{50}	Chu et al., 1982b
Sprague-Dawley rats	M	1196 mg/kg (corn oil)	intraperitoneal LD_{50}	Agarwal and Mehendale, 1983
Mammals	NR	9274 mg/kg (NR)		Sax, 1984
Mammals	NR	12,100 mg/m^3 (NR)	inhalation LC_{50}*	Sax, 1984

*Length of exposure not specified

NR = Not reported

values, histological changes in the kidneys and an activation of microsomal AH activity in females (Chu et al., 1982b); and numerous liver abnormalities defined in part by an increase in lipid diene conjugates (Reynolds, 1972), abnormal endoplasmic reticulum (Nishimura et al., 1980), increase in microsomal protein and RNA (Moody et al., 1981), decrease in protein content in males (Chu et al., 1982b), enlargement (Chu et al., 1980), and a decrease in cytochrome P450 and ALA-dehydratase levels and an increase in porphyrin and glutathione levels (Moody and Smuckler, 1986). A decrease in GSH in rats was reported by Pohl et al. (1980a).

Acute oral administration of bromoform to mice resulted in ataxia and lethargy (Bowman et al., 1978; NTP, 1988); fatty infiltration of the liver, pale kidneys and hemorrhaging of the lungs, adrenals and brain (Bowman et al., 1978); inhibited renal slice uptake of PAH, elevated SGPT values and numerous kidney and liver abnormalities (Condie et al., 1983); decrease in prothrombin time, glucose and BUN levels, an increase in SGOT and body weight and a significant depression in humoral and cell immunity (males), and decreased body weight and relative and absolute spleen weights as well as an increase in SGOT (females) (Munson et al., 1982). In addition, an increase in relative and absolute liver weights for both sexes was reported by Munson et al. (1982). Borzelleca (1983) also reported "significant findings" in the liver, kidney and thymus of adult male CD-1 mice after administration of bromoform by gavage at a level of 0.2, 125 or 250 mg/kg/day for 14 days.

Other routes of administration were studied by several investigators. Lucas (1928) reported liver damage (fatty degeneration, swelling of portal zone cells, necrosis and proliferation of fibrous connective tissues) in rabbits after bromoform administration through the rectum. Acute inhalation

exposure resulted in deep narcosis and death in a dog exposed to a level of 29,000 ppm for 1 hour (Sax, 1984), and disorders in the central nervous system in rabbits exposed to a concentration of 11-13 mg/ℓ (11,000-13,000 mg/m³) (time not specified in the abstract) and a protective inhibition of the cerebral cortex, disorders in protein metabolism and glycogen synthesis in the liver, disorders of filtration capacity of the kidneys, and vascular disorders and dystrophic changes in the liver and kidneys of rats exposed to vapors at a concentration of 2.5 mg/ℓ (2500 mg/m³) for 10 days (Dykan, 1964).

In addition, neural and behavioral toxicity was investigated. Parra et al. (1986) reported an increase in the central aminergic metabolic activity in the brain in fasted male Sprague-Dawley rats administered bromoform in .5 mℓ water by gavage. In a study in which adult male ICR mice were administered bromoform in a 1:8 Emulphor:water mixture by gavage at 0.9 or 9.2 mg/kg/day, Balster et al. (1979) and Balster and Borzelleca (1982) reported no observed behavioral effects following either a single dose or a series of 14 doses.

Agarwal and Mehendale (1983) and Klingensmith and Mehendale (1981) tested the potentiation of chlordecone on bromoform toxicity and concluded that bromoform is not a potent hepatotoxin and that chlordecone does not potentiate its effects. Hopkins and Krantz (1968) reported that an intravenous dose of bromoform as an oil-in-water mixture sensitized female mongrel dog myocardium to epinephrine.

Koyama and Nakazawa (1986) reported that bromoform inhibited the incorporation of [³H]glycerol into triacylglycerol in an *in vitro* lipid metabolism experiment with male Wistar rat liver slices. Mochida and Yamasaki (1984) reported an inhibitory effect from bromoform on growth of cultured

human cells and African green monkey kidney cells. Fraga et al. (1987) reported a significantly greater amount of thiobarbituric acid-reactive substances released from kidney slices incubated with bromoform. This release is a measure of lipid peroxidation. Kroneld (1987) determined that bromoform reduced phytohaemaglutinine stimulation in human peripheral blood lymphocytes and decreased the viability of human uroepithelial cells.

6.2. CARCINOGENICITY

6.2.1. Inhalation. Pertinent data regarding the inhalation carcinogenicity of bromoform were not located in the available literature cited in Appendix A.

6.2.2. Oral. There was no evidence of carcinogenicity in a feed study with male and female Wistar rats exposed for 24 months to microencapsulated bromoform (Kurokawa, 1987). Further information on this study was not available. In a study sponsored by NTP (1988), groups of 50 male and 50 female F344/N rats and 50 male and 50 female B6C3F1 mice were administered bromoform in corn oil 5 days/week for 2 years by oral gavage at levels of 0 (vehicle control), 100 or 200 mg/kg (rats and female mice) or at levels of 0 (vehicle control), 50 or 100 mg/kg (male mice) (see Section 6.1.2.). Neoplastic lesions (edenomatous polyps or adenocarcinomas) attributed by NTP (1988) to bromoform were observed in the large intestine of three male rats in the high-dose group, one female rat in the low-dose group and eight female rats in the high-dose group (Table 6-2). No neoplastic lesions were observed in the treated mice or in the vehicle control groups (Table 6-3). The lower incidence of lesions in the high-dose male rats compared with high-dose females may be due to the reduced survival of this group of animals. Survival was reduced significantly at 91 weeks and the first large intestinal tumor was not seen until 71.3 weeks. Bromoform was not

TABLE 6-2

Incidence of Tumors of the Large Intestine in F344/N Rats Treated by Gavage with Bromoform (≥95% pure) in Corn Oil for 103 Weeks[a]

Sex	Exposure	Body Weight (kg)	Tumor Incidence (p value)
M	vehicle control	0.450	0/50 (p=0.008)[b] (p=0.030)[c]
M	100 mg/kg, 5 days/week (71.4 mg/kg/day)	0.425	0/50
M	200 mg/kg, 5 days/week (142.9 mg/kg/day)	0.350	3/50 (p=0.028)[b] (p=0.092)[c]
F	vehicle control	0.250	0/50 (p<0.001)[b] (p<0.001)[c]
F	100 mg/kg, 5 days/week (71.4 mg/kg/day)	0.250	1/50 (p=0.461)[b] (p=0.461)[c]
F	200 mg/kg, 5 days/week (142.9 mg/kg/day)	0.225	8/50 (p=0.003)[b] (p=0.004)[c]

QUALITY OF EVIDENCE

Strengths of Study: Compound of acceptable purity administered to both sexes by a relevant route at two dose levels; adequate number of animals initiated; adequate duration of exposure; comprehensive histopathological and statistical analysis. Other nonneoplastic observations suggest the MTD had been reached or exceeded.

Weaknesses of Study: Nonnatural mode of administration; reduced survival in high-dose males.

Overall Adequacy: Adequate

[a]Source: NTP, 1988

[b]p values for Life Table Test

[c]p values for Logistic Regression Tests

TABLE 6-3

Incidence of Tumors of the Respiratory Tract in
B6C3F1 Mice Treated by Gavage with Bromoform (≥95% pure) in
Corn Oil for 103 Weeks[a]

Sex	Exposure	Body Weight (kg)	Tumor Incidence (p value)
M	vehicle control	0.40	11/50 (p=0.012)[b] (p=0.009)[c]
F	vehicle control	0.38	8/50
M	50 mg/kg, 5 days/week (35.7 mg/kg/day)	0.40	7/50 (p=0.288)[b] (p=0.236)[c]
M	100 mg/kg, 5 days/week (71.4 mg/kg/day)	0.40	2/49 (p=0.015)[b] (p=0.015)[c]
F	100 mg/kg, 5 days/week (71.4 mg/kg/day)	0.34	3/50
F	200 mg/kg, 5 days/week (142.9 mg/kg/day)	0.32	2/50 (p=0.60)[b] (p=0.49)[d]

QUALITY OF EVIDENCE

Strengths of Study: Compound of acceptable purity administered to both sexes by a relevant route at two dose levels; adequate number of animals initiated; adequate duration of exposure; comprehensive histopathological and statistical analysis. Other nonneoplastic observations suggest the MTD had been reached or exceeded.

Weaknesses of Study: Nonnatural mode of administration; reduced survival in treated females.

Overall Adequacy: Adequate

[a]Source: NTP, 1988

[b]p values for Life Table Test

[c]p values for Logistic Regression Tests

[d]p values for Fisher Exact Test

carcinogenic to the kidneys of rats or mice. NTP (1988) concluded that there was "some evidence of carcinogenic activity of bromoform for male F344/N rats and clear evidence of carcinogenic activity for female F344/N rats, based on increased incidence of uncommon neoplasms of the large intestine." There was no evidence of carcinogenic activity in the mice. The authors speculated that the high reactivity of the dibromocarbonyl active intermediate caused it to react with cellular nucleophiles too rapidly to permit DNA acylation, which would otherwise result in neoplasms.

6.2.3. Other Relevant Information. Kraybill (1983) lists bromoform as a suspected human carcinogen present in drinking water. According to Cantor et al. (1978), there is a positive correlation between levels of trihalomethanes in drinking water and the incidence of several human cancers including bladder and brain cancers in both sexes and non-Hodgkins lymphoma and kidney cancer in males. Bromoform produced a statistically significant ($p<0.041$) increase in the number of pulmonary adenomas/mouse in strain A mice following a total of 23 thrice-weekly intraperitoneal injections of the test substance in Tricaprylin at a level of 48 mg/kg/injection (Theiss et al., 1977); however, no increase was observed at 100 mg/kg. There was no effect on survival. Pereira et al. (1982a,b) determined that bromoform did not initiate GGTase-positive foci in the rat liver GTase-transformation test at 1 mmol (253 mg)/kg or 0.8 mmol (202 mg)/kg following a 2/3 partial hepatectomy and promotion with phenobarbital. Pereira et al. (1982a) stated, however, that carcinogens such as bromoform may have epigenetic rather than genotoxic mechanisms of action. Pereira (1983) also determined that bromoform is a potent inducer of ornithine decarboxylase induction activity. Ornithine decarboxylase is an apparent prerequisite and a potential molecular marker for tumor production in the skin and liver.

6.3. MUTAGENICITY

The results of several mutagenicity and genotoxicity assays with bromoform are presented in Table 6-4. Bromoform was mutagenic in Salmonella strains TA100 and TA1535 in the absence of metabolic activation when the assay was conducted in a desiccator (Simmon, 1977), but not in a "standard" preincubation assay (NTP, 1988). Positive gene mutation responses were also reported in the mouse lymphome L5178Y TK forward mutation assay in the absence of activation (NTP, 1988) and in the Drosophila sex-linked recessive lethal assay by feeding but not by injection (Woodruff et al., 1985).

Bromoform was positive in the sister chromatid exchange (SCE) assay in human lymphocytes treated in culture (Morimoto and Koizumi, 1983) and marginally positive in CHO cells in one of two laboratories without but not with rat liver S9 activation (Galloway et al., 1985). Induction of SCEs was also reported in mouse bone marrow cells (Morimoto and Koizumi, 1983; NTP, 1988). The results in the chromosome aberration assay in CHO cells were as for SCE; the same laboratory reported the high dose marginally positive in the absence of metabolic activation (Galloway et al., 1985). Bromoform was negative for chromosome aberrations but positive for micronuclei in bone marrow cells of mice receiving single i.p. injections.

6.4. TERATOGENICITY

Ruddick et al. (1983) administered bromoform (96% pure) dissolved in corn oil by gavage to groups of 15 mated Sprague-Dawley rats at a level of 0 (vehicle control), 50, 100 or 200 mg/kg/day from day 6-15 of gestation. Extensive clinical and histological parameters examined in the dams included: body weight; an extensive hematological profile; liver, heart, brain, spleen and kidney weights; and the presence of lesions in a large number of organs. No evidence of maternal toxicity was observed. On day 22

TABLE 6-4

Mutagenicity Testing of Bromoform

Assay	Indicator/ Organism	Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	Salmonella typhimurium TA97 TA98, TA1535 TA100, TA1537	NR	pre-incubation	0-6666 µg/plate 0-6666 µg/plate 0-1000 µg/plate	±S-9 ±S-9 ±S-9	- - -	Equivocal results reported sporadically in some trials	NTP, 1988
Reverse mutation	S. typhimurium TA1535	NR	in dessicator	0-200 µl/dessicator	-S-9	+	NC	Simmon, 1977a
	TA100		in dessicator	0-200 µl/dessicator	-S-9	+	NC	Simmon, 1977a
Forward mutation	mouse L5178Y cells at TK locus	NR	suspension	0-300 µg/ml	-S9	+	Positive at concentrations between 200 and 250 nl/ml without metabolic activation (~300 nl/ml was lethal).	NTP, 1988
				0-50 µg/ml	+S9	?	Positive at concentrations of 25 nl/ml with activation (~50 nl/ml was lethal) but not statistically significant	
Induction of SCE	Chinese hamster ovary cells	NR	cell culture	16-968 µg/ml	±S-9	±	Weakly positive	Galloway et al., 1985
Induction of SCE	human lymphocytes (in vitro)	NR	dissolved in DMSO, added to cell culture	1.6×10^{-5} to 5×10^{-3} M	NR	+	All doses tested delayed the cell cycle. SCE induction was dose dependent.	Morimoto and Koizumi, 1983
Induction of SCE	ICR/SJ mouse bone marrow cells (in vivo)	NR	fed as olive oil mixture once a day for 4 days (0.2 ml)	25 or 200 mg/kg/day	NA	‡	NC	Morimoto and Koizumi, 1983
Induction of SCE	male B6C3F1 mice bone marrow cells	NR	intraperitoneal injection in corn oil	200, 400, 800 mg/ml	NA	+	NC	NTP, 1988

TABLE 6-4 (cont.)

Assay	Indicator/ Organism	Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Induction of Chromosomal aberrations	Chinese hamster ovary cells	NR	cell culture	50-1070 µg/mℓ	±S-9	±	Weakly positive	Galloway et al., 1985
Induction of chromosomal aberrations	male B6C3F1 mice bone marrow cells	NR	intraperitoneal injection in corn oil	200, 400, 800 mg/kg	NA	-	NC	NTP, 1988
Reciprocal translocation	Drosophila melanogaster	97.7% pure	feed in 5% sucrose	3000 ppm	NA	-	NC	Woodruff et al., 1985
Sex-linked recessive mutation	adult Canton-S male Drosophila melanogaster	97.7% pure	feed in 5% sucrose	0 or 3000 ppm	NA	+	NC	Woodruff et al., 1985
			injected in 0.7% saline	0 or 1000 ppm	NA	-	NC	Woodruff et al., 1985
Incidence of micronuclei in bone marrow polychromatic erythrocytes	B6C3F1 mice	NR	intraperitoneal injection in corn oil	0, 200, 400, 800 mg/kg	NA	+	NC	NTP, 1988

NA = Not applicable; NC = no comment; NR = not reported

of gestation fetuses were removed, weighed and examined for viability, external malformations, histological parameters, skeleton abnormalities and visceral changes. Bromoform had no effect on survival or fetal weight and there was no evidence of a teratogenic effect but there was evidence of a fetotoxic response. Although statistical analysis was not performed, it appeared that there was an increase in the number of litters with sternebral abberrations at 100 and 200 mg/kg/day. No developmental effects were observed at 50 mg/kg/day.

6.5. OTHER REPRODUCTIVE EFFECTS

Borzelleca (1983) reported that intratesticular administration of bromoform at a level of 100-1400 mg/kg to male CD-1 mice resulted in inhibition of testicular DNA synthesis.

6.6. SUMMARY

The liver, kidneys and central nervous system appear to be important target organs for bromoform toxicity. Both inhalation (Dykan, 1962, 1964) and oral (NTP, 1988; Chu et al., 1982a,b; Borzelleca, 1983) administration result in abberrations in morphology or function of these organs. Hepatocellular vacuolization was found in both male mice ($\geq$200 mg/kg/day) and male rats ($\geq$50 mg/kg/day) in a subchronic study (13 weeks, 5 days/week) and in female mice ($\geq$100 mg/kg/day) in a chronic study (103 weeks, 5 days/week) sponsored by NTP (1988). Compound-related mortality was observed in male rats (200 mg/kg/day) in the chronic study. Also, narcosis (Sax, 1984) and lethargy (Bowman et al., 1978; Chu et al., 1980; NTP, 1988) were observed in animals receiving bromoform by inhalation and oral routes, respectively. Altered RES function was observed in male and female mice receiving bromoform at a level of 125 mg/kg/day for 90 days by gavage (Munson et al., 1977,

1978). Operant behavior was impaired after administration of bromoform to mice at levels of 100 and 400 mg/kg/day for 60 days (Balster and Borzelleca, 1982).

NTP (1988) concluded that there was "some evidence of carcinogenicity of bromoform for male F344/N rats and clear evidence...for female F344/N rats." Female rats at 200 mg/kg/day displayed a higher incidence of neoplastic lesions of the large intestine compared with male rats and untreated controls (NTP, 1988). This may be due in part to the fact that male rats had reduced survival rates compared with females at equal doses (NTP, 1988). Bromoform tested positive for mutagenicity in both *in vivo* and *in vitro* assays (NTP, 1988). Bromoform did not produce teratogenic effects, but did produce fetotoxic effects in rats treated at 100, but not at 50 mg/kg/day (Ruddick et al., 1983).

Information exists on the effects of bromoform and other trihalomethane contamination in drinking water on humans; however, this information is considered incomplete and preliminary because there are several unaddressed variables (NTP, 1988).

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The recommended TLV for bromoform is 0.5 ppm (5 mg/m³), with a skin designation, based on the chemical's irritant qualities (ACGIH, 1986). OSHA (1985) established a PEL of 0.5 ppm (5 mg/m³). U.S. EPA (1987b) reported an RfD for bromoform of 2×10^{-2} mg/kg/day based on the NOAEL for hepatic lesions of 25 mg/kg/day in the subchronic NTP (1988) study, and an interim maximum contaminant level for drinking water of 0.10 mg/ℓ for total trihalomethanes. The latter value is based on the chronic toxicity of chloroform.

U.S. EPA (1982) derived an ambient water quality criterion of 0.19 mg/ℓ for bromoform based on an uncertainty factor of 1000, an ADI of 0.39 mg/day (based on a study by Chu et al., 1982a), a daily water and contaminated fish consumption of 2 ℓ/day and 0.0065 kg/day, respectively, and a BCF of 7.0 ℓ/kg.

Based on chronic toxicity, the RQ value for release into the environment is 100 pounds (U.S. EPA, 1987b, 1988).

7.2. AQUATIC

Guidelines and standards for the protection of aquatic life from exposure to bromoform were not located in the available literature cited in Appendix A.

8. RISK ASSESSMENT

8.1. CARCINOGENICITY

8.1.1. Inhalation. Pertinent data regarding the inhalation carcinogenicity of bromoform in humans or animals were not located in the available literature cited in Appendix A.

8.1.2. Oral. NTP (1988) sponsored a gavage study with 50 male and 50 female F344/N rats and 50 male and 50 female B6C3F1 mice. Neoplastic lesions (adenomatous polyps or adenocarcinomas) attributed to bromoform were found in the large intestines of three male rats receiving bromoform 5 days/week for 2 years at a level of 200 mg/kg/day, one female rat receiving 100 mg/kg/day and eight female rats receiving 200 mg/kg/day. There were no lesions of this type in the vehicle control group.

Kraybill (1983) lists bromoform as a suspected human carcinogen in drinking water. According to Cantor et al. (1978), there is a positive correlation between levels of trihalomethanes in drinking water and the incidence of several human cancers.

8.1.3. Other Routes. Theiss et al. (1977) reported an increase ($p<0.04$) in the number of pulmonary adenomas in strain A mice following 23 intraperitoneal injections of the test substance in Tricaprylin at a level of 48 mg/kg/injection. There was no significant difference in the number of lung tumors in mice administered bromoform at a level of 4 mg/kg/injection for 18 injections or 100 mg/kg/injection for 24 injections.

8.1.4. Weight of Evidence. Although studies pertaining to human cancer risk and drinking water contamination exist, these studies group many halomethanes together and fail to consider circumstances such as exposure to other potential carcinogens, family history and lifestyle. The human data may be best considered "inadequate." The evidence for carcinogenicity in

animals is sufficient because studies in two species (rats and mice) demonstrated an increase in cancer incidence after oral or intraperitoneal administration of bromoform. Therefore, according to the U.S. EPA (1986) guidelines for carcinogenic risk assessment, bromoform should be assigned to EPA Group B2, a probable human carcinogen. This assessment is supported by positive results in mutagenicity tests and by the carcinogenicity of structurally related compounds.

8.1.5. Quantitative Risk Assessment.

8.1.5.1. **INHALATION** -- Appropriate inhalation exposure data were not located from which to estimate the carcinogenic potency for inhalation exposure to bromoform. A q_1^* of 7.9×10^{-3} $(mg/kg/day)^{-1}$ was estimated for humans orally exposed to bromoform based on an increased incidence of neoplasms of the large intestine in female rats treated by gavage (Section 8.1.5.2.). Several factors suggest that the tumorigenic response observed in the large intestine may be a systemic rather than a portal-of-entry effect. The mutagenicity data (see Section 6.3.) indicate that metabolism with mammalian S-9 is necessary for a genotoxic response in microorganisms and mammalian cell cultures. Pharmacokinetic data suggest that gastrointestinal absorption is rapid (see Section 5.1.) and that biotransformation is an activating mechanism (see Section 5.3.). Conversely, while the liver has been shown to metabolize bromoform by way of dibromocarbonyl, some of the evidence indicates that liver metabolites may not be completely responsible for tumor induction. While a much greater fraction of bromoform was metabolized by mice, only rats showed significant carcinogenic response. Furthermore, the tumor site was in the gastrointestinal tract, an early site of contact. Nothing in the pharmacokinetic studies rules out bromoform or an active intermediate metabolized by the intestinal cells as an ultimate carcinogen.

When possible, the best approach to route-to-route extrapolation for estimating cancer potency for chemicals requiring metabolic activation is to base the estimation on a metabolized dose rather than an exposed or internal dose. Kinetic data for the metabolism of bromoform are insufficient, however, to estimate route-specific metabolized doses. It is possible that lesser metabolism would occur following inhalation exposure because of the absence of the "first pass" phenomenon. If so, the estimate of inhalation cancer potency based on the oral study may be unnecessarily stringent and guidelines derived therefrom may be overly protective. In the NTP (1988) study, bromoform was given in corn oil. If the bromoform was absorbed with the corn oil into the lymphatics, bypassing the hepatic portal system, it is possible that the metabolism of bromoform in this study may approximate that expected from inhalation exposure.

On the other hand, the metabolic studies were based upon a bolus dose of bromoform. The rats in those studies metabolized a much smaller fraction of the compound than mice and exhaled it through the lungs much more rapidly. This indicates that metabolism of bromoform is fairly slow and that, in rats at least, most of it is exhaled before it could be metabolized to an active form. When given by inhalation, however, bromoform will remain in the body as long as exposure continues. This allows many passes through the liver and assures that a greater percentage of the compound will be activated. For this reason, it seems likely that the potency by inhalation would be underestimated using oral exposure data. Because of the uncertainties associated with the metabolism and the mechanism of bromoform activity in tumor induction, estimation of a q_1^* for inhalation exposure by extrapolation from oral data is not recommended.

8.1.5.2. ORAL -- The cancer risk assessment for exposure to bromoform is based on an oral exposure study (NTP, 1988) in which an increased incidence of neoplasms was observed in the large intestine of treated female rats (see Table 6-2). Derivation of a cancer potency estimate (q_1*) is presented in Appendix B. The equivalent human dosages estimated in Appendix B are derived from the transformed animal doses multiplied by the cube root of the ratio of the estimated group mean animal body weight to the assumed human body weight (70 kg), then further multiplied by the cube of the ratio of length of exposure (103 weeks) to the assumed lifespan of the animal (104 weeks) (U.S. EPA, 1980b). The q_1* generated by the Howe and Crump (1982) multistage model based on equivalent human dosages is 7.9×10^{-3} (mg/kg/day)-1, which is an estimate of excess cancer risk to exposed humans. The pharmacokinetic data indicate that gastrointestinal absorption in rats is $\geq$78.9%. In the absence of more definitive data, it is assumed that gastrointestinal absorption is 100%. Therefore, this q_1* of 7.9×10^{-3} $(mg/kg/day)^{-1}$ for oral exposure is considered to be the cancer potency based on internal dose. The concentrations of the chemical in drinking water associated with an increased lifetime risk of cancer of 10^{-5}, 10^{-6} and 10^{-7} are 4.4×10^{-2}, 4.4×10^{-3} and 4.4×10^{-4} mg/ℓ respectively. These values were derived by dividing the corresponding risk levels by the q_1*, correcting for the assumed human body weight of 70 kg and the assumed daily intake of water of 2 ℓ.

8.2. SYSTEMIC TOXICITY

8.2.1. Inhalation Exposure.

8.2.1.1. LESS THAN LIFETIME EXPOSURES -- Dykan (1962) briefly reported disorders in the glycogenesis and protein prothrombim functions of the liver and filtration capacity of the kidneys of rats exposed to bromoform at a level of 250 mg/m³, 4 hours/day for 2 months. This inhalation

exposure expanded over a 24-hour period and a 7-day week corresponds to a dosage of 26.5 mg/kg/day. Because of inadequate reporting of this study, a subchronic inhalation RfD cannot be derived.

8.2.1.2. CHRONIC EXPOSURES -- Dykan (1964) briefly reported that the threshhold concentration for chronic exposure to bromoform was 50 mg/m^3 for rats. He also stated that humans occupied with bromoform production exhibited changes in the central nervous system and liver. The experimental protocol was not reported and an inhalation dosage cannot be derived from these data.

8.2.2. Oral Exposure.

8.2.2.1. LESS THAN LIFETIME EXPOSURES -- Subchronic oral exposure studies exist for male and female rats and male and female mice. In a study sponsored by NTP (1988), lethargy was present in male rats administered bromoform by gavage for 13 weeks at dose levels $\geq$100 mg/kg and in female rats given 200 mg/kg. All of the male rats given 200 mg/kg had diarrhea. Hepatocellular vacuolization was present at a level greater than that of the vehicle control group in male rats at all doses $\geq$12 mg/kg. The vacuoles were more numerous in the liver cells of high-dose rats, however, and statistical significance was present at levels $\geq$50 mg/kg for 5 days/week (35.7 mg/kg/day). No significant effects were observed at levels $\leq$25 mg/kg for 5 days/week (17.9 mg/kg/day). NTP (1988) also reported dose-related cytoplasmic vacuolization of hepatocytes in male mice receiving 200 or 400 mg/kg/day for 13 weeks.

Chu et al. (1982b) reported a slight increase in relative kidney weights in male Sprague-Dawley rats administered bromoform in drinking water at a level of 500 ppm, but not at 50 ppm, for 28 days.

Munson et al. (1977) reported a decrease in blood clearance of I^{125}-labeled L. monocytogenes in male mice receiving bromoform at a level of 0.2 mg/kg/day for 90 days by oral gavage. A dose-related depression in specific activity of L. monocytogenes in the liver was observed in females and males receiving bromoform at a level of 125 mg/kg/day (Munson et al., 1977, 1978). The decrease in blood clearance and specific activity in the liver indicated a reduced uptake and disposal of phagocytic cells. Munson et al. (1977) concluded that there was a slight alteration in RES function.

Operant behavior was impaired in male ICR mice administered bromoform by gavage at a level of 100 and 400 mg/kg/day for 60 days (Balster and Borzelleca, 1982).

Chu et al. (1982a) reported significantly decreased lymphocyte counts in male and female Sprague-Dawley rats exposed to bromoform in drinking water at a level of 2500 ppm for 90 days with a 90-day recovery period. Suppressed food consumption was observed in male rats exposed to 2500 ppm. Mild histological changes in the liver and thyroid were observed in both male and female rats at all dose levels between 5 and 2500 ppm, but were more severe and occurred at a higher frequency at levels $\geq$500 ppm. These effects were not apparent after the 90-day recovery period.

No effects were observed in male CD-1 mice administered bromoform in drinking water up to a level of 250 mg/kg/day for 90 days (Borzelleca, 1983). Also, Schuller et al. (1978) reported no effects on hypersensitivity, humoral immune response, liver function, kidney function or hematology in male and female ICR mice administered bromoform by gavage at a dose up to 125 mg/kg/day for 90 days.

The study most suitable for an RfD determination is the 13-week study sponsored by NTP (1988). This study provides the highest NOAEL below which there is no LOAEL. From the NTP (1988) study, the NOAEL for male rats (the

most sensitive subjects in this study) was 25 mg/kg, 5 days/week for 13 weeks (17.9 mg/kg/day). Statistically significant hepatocellular vacuolization was not present at this level but was present at levels ≥50 mg/kg for 5 days/week (35.7 mg/kg/day). Chu et al. (1982a) also reported liver effects at levels ≥500 ppm (70 mg/kg) for 90 days. The subchronic oral RfD is 0.179 mg/kg/day (17.9 mg/kg/day divided by an uncertainty factor of 100; 10 for interspecies extrapolation multiplied by 10 to provide additional protection for more sensitive individuals). The subchronic oral RfD is most appropriately rounded to 0.2 mg/kg/day, or 13 mg/day for a 70 kg human. Medium confidence is placed in this RfD. NTP (1988) used both sexes of two animal species and both species had the liver lesions used to derive the NOAEL.

8.2.2.2. **CHRONIC EXPOSURE** -- Ruddick et al. (1983) administered bromoform (96% pure) dissolved in corn oil by gavage to groups of 15 mated Sprague-Dawley rats at a level of 0 (vehicle control), 50, 100 or 200 mg/kg/day from day 6-15 of gestation. The Agency considers this to be chronic exposure to fetuses. Extensive clinical and histopathological examinations revealed no evidence of teratogenesis but there was evidence of fetotoxicity. Although no statistical analysis was reported, it appeared that there was an increase in the number of litters with sternebral abberrations at 100 and 200 mg/kg/day. The NOAEL for developmental effects was 50 mg/kg/day.

In a chronic gavage study sponsored by NTP (1988), 50 male and 50 female rats and 50 female mice were administered bromoform at levels of 0, 100 or 200 mg/kg, and 50 male mice were administered the test substance at levels of 0, 50 or 100 mg/kg, 5 days/week for 103 weeks. Compound-related deaths were observed in male rats receiving 200 mg/kg/day; lethargy was observed in treated male and female rats; aggressiveness was observed in treated male rats; and decreased mean body weights were observed in high-dose males and

females. Nonneoplastic lesions were observed in dosed rats of both sexes; increased mixed cell foci, decreased basophilic foci and decreased necrosis of the liver were observed in dosed females (compared with controls); and liver lesions and increased gastric ulcers and chronic inflammation of the lung were observed in dosed males.

Mean body weights of dosed female mice were decreased, follicular cell hyperplasia of the thyroid gland was observed in dosed females, cytoplasmic vacuolization of hepatocytes was observed in high-dose females and hyperplasia of the glandular stomach was observed in dosed males.

The LOAEL in this study is 50 mg/kg/day for 5 days/week (35.7 mg/kg/day). Hyperplasia of the glandular stomach was observed in male mice at this level. Since no lower dose levels were evaluated, a NOAEL does not exist. The subchronic data provide a NOAEL of 17.9 mg/kg/day that is supported by the chronic data. The subchronic oral RfD of 0.2 mg/kg/day can serve as the basis for the RfD for chronic oral exposure by application of an additional factor of 10 to expand from subchronic to chronic exposure. Therefore, the RfD for oral exposure is 0.02 mg/kg/day. Moderate confidence is placed in this RfD because of the lack of a threshhold level for chronic exposure. The verified oral RfD presented in IRIS (U.S. EPA, 1987b) is also 2×10^{-2}. This RfD was also derived from subchronic data before chronic data were available; an uncertainty factor of 1000 was applied.

8.3. AQUATIC

Insufficient data prevented the development of criteria for the protection of freshwater (Figure 8-1) and marine (Figure 8-2) life exposed to bromoform. Development of a freshwater criterion requires the results of acute assays with a salmonid fish species, a benthic crustacean, a non-Arthropod/Chordate, and a new insect or phylum representative. Results from chronic assays required for the development of a freshwater criterion

Family	TEST TYPE		
	Acute[a]	Chronic[a]	BCF[a]
#1 Chordate (Salmonid-fish)	NA	NA	NA
#2 Chordate (warmwater fish)	29[b]	NA	NA
#3 Chordate (fish or amphibian)	52[b]	NA	NA
#4 Crustacean (planktonic)	45.2[d]	NA	NA
#5 Crustacean (benthic)	NA,	NA	NA
#6 Insectan	75[e]	NA	NA
#7 non-Arthropod/-Chordate	NA	NA	NA
#8 New Insectan or phylum representative	NA	NA	NA
#9 algae	NA	114[f]	NA
#10 Vascular plant	NA	NA	NA

[a]NA = Not available; [b]96-hour LC_{50} in mg/ℓ with bluegill sunfish, Lepomis macrochirus; [c]LC_{50} in mg/ℓ for carp embryos, Cyprinus carpio; [d]48-hour LC_{50} in ppm for Daphnia magna and 96-hour LC_{50} in mg/ℓ for Daphnia pulex; [e]24-hour LC_{50} in ppm for larval mosquitoes, Aedes aegypti; [f]96-hour EC_{50} in ppm for Selanastrum capricornutum

FIGURE 8-1

Organization chart for listing FMAVs required to derive numerical water quality criteria by the method of EPA/OWRS (1986) for the protection of freshwater aquatic life exposed to bromoform

Family	TEST TYPE		
	Acute[a]	Chronic[a]	BCF[a]
#1 Chordate	12[b]	NA	NA
#2 Chordate	11.3[c]	6.39[d]	NA
#3 non-Arthropod/-Chordate	NA	NA	NA
#4 Crustacean (Mysid/Panaeid)	24.4[e]	NA	NA
#5 non-Chordate	>40[f]	NA	NA
#6 non-Chordate	>40[g]	NA	NA
#7 non-Chordate	>40[h]	NA	NA
#8 other	28[i]	NA	NA
#9 algae	NA	11.9[j]	NA
#10 Vascular plant	NA	NA	NA

[a]NA = Not available; [b]96-hour LC_{50} in mg/ℓ for menhaden, Brevoortia tyranus; [c]96-hour LC_{50} in mg/ℓ for sheepshead minnow, Cyprinidon variegatus; [d]MATC in mg/ℓ for sheepshead minnow, C. variegatus; [e]96-hour LC_{50} in ppm for Mysidopsis bahia; [f]96-hour LC_{50} in mg/ℓ for the clam, Mercenaria mercenaria; [h]96-hour LC_{50} in mg/ℓ for the oyster, Crassostrea virginica; [i]96-hour LC_{50} in mg/ℓ for the shrimp, Penaeus aztecus; [j]96-hour EC_{50} in ppm for Skeletonema costatum

FIGURE 8-2

Organization chart for listing FMAVs required to derive numerical water quality criteria by the method of EPA/OWRS (1986) for the protection of saltwater aquatic life from exposure to bromoform

include assays with two species of fauna and at least one bioconcentration study. Development of a saltwater criterion requires the results of an acute assay with a non-Arthropod/Chordate species. Results from chronic assays required for the development of a saltwater criterion include an assay with one species of fauna and at least one bioconcentration study.

9. REPORTABLE QUANTITIES

9.1. BASED ON SYSTEMIC TOXICITY

The effects of oral and inhalation exposure to bromoform were discussed in Chapter 6. Dose-response data for toxicologically significant effects in studies of sufficient quality and duration suitable for RQ derivation are summarized in Table 9-1. As noted in Table 9-1, oral administration of bromoform to animals has resulted in liver lesions, lethargy, diarrhea, impaired operant behavior, changes in hematology, low body weight, feto-toxicity and increased mortality.

Several possible CSs and corresponding RQs are derived in Table 9-2. In computing the chronic human MED from the human equivalent dose in the subchronic studies, no uncertainty factor was applied to expand to chronic exposure, because the NTP (1988) studies suggest little difference in toxic potency between subchronic and chronic exposure. CSs were not estimated for diarrhea (NTP, 1988), which was considered to be an acute manifestation of gavage dosing, nor for reduced lymphocyte count (Chu et al., 1982a), which occurred only during the recovery period and is of uncertain toxicologic significance. A CS for lethargy was calculated for males in the subchronic NTP (1988) study and not for females in the chronic NTP (1988) study because the males in the subchronic study had lower body weights, which would result in the higher RV_d. A CS for liver lesions was calculated from the NTP (1988) subchronic study, but not from the Chu et al. (1982a) study because the lower human equivalent dose was estimated from the NTP (1988) study.

The most severe effect is reduced survival in the NTP (1988) chronic study. This corresponds to an RV_e of 10. A chemical-related increase in mortality was observed in male rats administered bromoform at a level of 200 mg/kg/day, 5 days/week for 103 weeks, which corresponds to an equivalent

TABLE 9-1

Toxicity Summary for Bromoform

Route	Species/ Strain	Sex	Number at Start	Average Body Weight (kg)	Vehicle	Purity	Exposure	Transformed Animal Dose (mg/kg/day)	Equivalent Human Dose[a]	Response	Reference
Oral gavage	rats/ F344/N	M	10	0.258[b]	corn oil	≥95%	100 mg/kg, 5 days/week for 13 weeks	71.4	11.0	lethargy	NTP, 1988
	rats/ F344/N	M	10	0.245[b]	corn oil	≥95%	200 mg/kg, 5 days/week for 13 weeks	143	21.7	diarrhea	NTP, 1988
	rats/ F344/N	M	10	0.260[b]	corn oil	≥95%	50 mg/kg, 5 days/week for 13 weeks	35.7	5.5	hepatocellular vacuolization	NTP, 1988
Drinking water	rats/ Sprague-Dawley	F	20	0.35[c]	Emulphor: water	NR	2500 ppm for 90 days	350[d]	59.8	decreased lymphocyte count	Chu et al., 1982a
							500 ppm for 90 days	70[d]	12.0	liver lesions	
Gavage	rats/ F344/N	M	50	0.425[b]	corn oil	≥95%	100 mg/kg, 5 days/week for 103 weeks	71.4	13.0	low body weight	NTP, 1988
		F	50	0.275[b]	corn oil	≥95%	100 mg/kg, 5 days/week for 103 weeks	71.4	11.3	lethargy	NTP, 1988
		F	50	0.350[b]	corn oil	≥95%	200 mg/kg, 5 days/week	143	24.5	increased mortality	NTP, 1988
Gavage	rats/ Sprague-Dawley	F	15	0.194[b]	corn oil	96%	100 mg/kg/day, days 6-15 of gestation	100	14.0	fetotoxicity	Ruddick et al., 1983
Gavage	mice/ICR	M,F	18, 23	0.03[e]	NR	NR	125 mg/kg/day for 90 days	125	9.4	decreased hepatic phagocytosis	Munson et al., 1977

TABLE 9-1 (cont.)

Route	Species/ Strain	Sex	Number at Start	Average Body Weight (kg)	Vehicle	Purity	Exposure	Transformed Animal Dose (mg/kg/day)	Equivalent Human Dose[a]	Response	Reference
Gavage	mice/ICR	M	6-8	0.03[e]	Emulphor: water	NR	100 mg/kg/day for 60 days	100	7.54	Impaired operant behavior	Balster and Borzelleca, 1982

[a]Calculated by multiplying the animal transformed dose by the cube root of the ratio of the animal body weight to the human body weight (70 kg)

[b]Estimated from growth curves or weight gain data in the study

[c]Reference rat body weight (U.S. EPA, 1980b)

[d]Calculated by multiplying the concentration by the reference water consumption rate for rats (0.049 ℓ/day) and dividing by the reference rat body weight (U.S. EPA, 1980b)

[e]Reference mouse body weight (U.S. EPA, 1980b)

NR = Not reported

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TABLE 9-2

Oral Composite Scores for Bromoform

Species/ Strain	Animal Dose (mg/kg/day)	Chronic Human MED* (mg/day)	RV_d	Effect	RV_e	CS	RQ	Reference
Rats/ F344/N	71.4	770	1.2	lethargy	7	8.4	1000	NTP, 1988
Rats/ F344/N	35.7	385	1.6	hepatocellular vacuolization	5	8	1000	NTP, 1988
Rats/ F344/N	71.4	910	1.1	low body weight	4	4.4	5000	NTP, 1988
Rats/ F344/N	143	1715	1	increased mortality	10	10	1000	NTP, 1988
Rats/ Sprague-Dawley	100	980	1	fetotoxicity	8	8	1000	Ruddick et al., 1983
Mice/ICR	125	658	1.3	decreased hepatic phagocytosis	6	7.8	1000	Munson et al., 1977, 1978
Mice/ICR	100	528	1.4	impaired operant behavior	7	9.8	1000	Balster and Borzelleca, 1982

*Calculation: Transformed animal dose (mg/kg/day) x [animal body weight (kg)/reference human body weight (70 kg)]$^{1/3}$

human dose of 24.5 mg/kg/day. Multiplied by the assumed human body weight of 70 kg, this becomes a MED of 1715 mg/day, which corresponds to an RV_d of 1. Multiplying the RV_e of 10 by the RV_d of 1 results in a CS of 10, which corresponds to an RQ of 1000 pounds (Table 9-3).

Other studies summarized in Table 9-2 resulted in lower CSs. Lethargy and low body weight were also reported in the NTP (1988) chronic study with rats. This occurred at a lower dose (higher RV_d) but was assigned a lower RV_e. Lethargy and hepatocellular vacuolization were also observed in rats in the subchronic NTP (1988) study. Although it occurred at the lowest dose, hepatocellular vacuolization was considered a relatively nonsevere effect. Likewise, the decreased hepatic phagocytosis observed in mice (Munson et al., 1977, 1978) was assigned a lower RV_e. Impaired operant behavior mice observed by Balster and Borzelleca (1982) was also evaluated as a less severe effect. The fetotoxicity in rats described by Ruddick et al. (1983) was a severe effect but resulted in a lower CS than the chronic NTP (1988) study.

U.S. EPA (1983) reported possible RQs of 100 or 1000 pounds. These RQs were derived from the decrease in hepatic phagocytosis at levels of 12.5 or 125 mg/kg/day, respectively, reported in the 90-day subchronic study by Munson et al. (1978). Also, the transformed animal doses of 12.5 and 125 mg/kg/day were divided by a factor of 10 to convert to a chronic value. The actual minimum effective dose is difficult to discern from these abstracts. Also, the toxicological significance of reduced hepatic phagocytosis is unclear. These data will not be used in quantitative risk assessment primarily because more comprehensive subchronic and chronic toxicity studies are available.

TABLE 9-3

Bromoform

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	gavage
Dose*:	1715 mg/day
Effect:	mortality
Reference:	NTP, 1988
RV_d:	1
RV_e:	10
Composite Score:	10
RQ:	1000 pounds

*Equivalent human dose

The current accepted RQ should be re-evaluated in light of the new data available from NTP (1988).

9.2. BASED ON CARCINOGENICITY

NTP (1988) evaluated the carcinogenicity of bromoform administered by gavage to male and female rats and female mice at levels of 0 (vehicle control), 100 or 200 mg/kg/day and to male mice at levels of 0, 50 or 100 mg/kg/day, 5 days/week for 103 weeks (see Section 6.2. and Table 6-2). Adenomatous polyps or adenocarcinomas were observed in the large intestines of three male rats receiving 200 mg/kg/day, one female receiving 100 mg/kg/day and eight females receiving 200 mg/kg/day. No tumors were observed in mice. Bromoform increased the number of pulmonary adenomas/mouse in the strain A assay at 48 mg/kg, but not at 100 mg/kg (Theiss et al., 1977). The compound was administered by intraperitoneal injection thrice weekly for 23 total injections. The evidence for carcinogenicity in animals is considered sufficient together with positive evidence in short-term tests, mutagenicity and structure-activity relationship with other B2 carcinogens such as $CHCl_3$ and $CHBrCl_2$. The evidence pertaining to human data is inadequate. Bromoform is assigned to EPA Group B2 (see Section 8.1.).

The potency factor (F factor) calculated using the incidences of neoplastic lesions in the female rats (NTP, 1988) and the computerized multistage model developed by Howe and Crump (1982) is 5.86294×10^{-2} $(mg/kg/day)^{-1}$ (Table 9-4). Because the F factor is <1, bromoform is placed in Potency Group 3. A Potency Group 3 chemical with an EPA classification of B2 corresponds to a LOW hazard rank under the CERCLA Hazard Ranking Scheme. Chemicals with a LOW hazard ranking are assigned an RQ of 100.

TABLE 9-4

Derivation of Potency Factor (F) for Bromoform

Reference:	NTP, 1988
Exposure route:	gavage
Species:	rats
Strain:	F344/N
Sex:	F
Vehicle or physical state:	corn oil
Body weight:	~0.250 kg*
Duration of treatment:	103 weeks
Duration of study:	103 weeks
Lifespan of animal:	104 weeks
Target organ:	large intestine
Tumor type:	adenomatous polyps and adenocarcinomas
Experimental doses/exposures:	0 (vehicle control), 100 or 200 mg/kg/day, 5 days/week
Equivalent human doses (mg/kg/day):	0, 10.6, 20.5
Tumor incidence:	0/50, 1/50, 8/50
Human $1/ED_{10}$ (F Factor):	0.058624 $(mg/kg/day)^{-1}$

*Estimated from graphs

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APPENDIX A

LITERATURE SEARCHED

This HEED is based on data identified by computerized literature searches of the following:

CHEMLINE
TSCATS
CASR online (U.S. EPA Chemical Activities Status Report)
TOXLINE
TOXLIT
TOXLIT 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register
CAS ONLINE (Chemistry and Aquatic)
HSDB

These searches were conducted in May 1988, and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1986. Documentation of the Threshold Limit Values and Biological Exposure Indices, 5th ed. Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). 1987. TLVs: Threshold Limit Values for Chemical Substances in the Work Environment adopted by ACGIH with Intended Changes for 1987-1988. Cincinnati, OH. 114 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. 2878 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B. John Wiley and Sons, NY. p. 2879-3816.

Clayton, G.D. and F.E. Clayton, Ed. 1982. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2C. John Wiley and Sons, NY. p. 3817-5112.

Grayson, M. and D. Eckroth, Ed. 1978-1984. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., Littleton, MA. 575 p.

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SRI (Stanford Research Institute). 1987. Directory of Chemical Producers. Menlo Park, CA.

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Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Windholz, M., Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under Contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

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Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. Prepared for the U.S. EPA, Washington, DC. PB-269605.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. Office of Pesticide Programs, U.S. EPA, Washington, DC. EPA 540/9-79-003. NTIS PB 80-196876.

APPENDIX B

Cancer Data Sheet for Derivation of q_1^*

Compound:	Bromoform
Reference:	NTP, 1988
Species, Strain, Sex:	Rat, F344/N, Female
Body Weight:	estimated from graphs
Length of exposure (le) =	103 weeks
Length of experiment (Le) =	103 weeks
Lifespan of animal (L) =	104 weeks
Tumor site and type:	large intestine, adenomatous polyps or adenocarcinomas
Route, Vehicle:	gavage, corn oil

Experimental Doses or Exposures (mg/kg/day, 5 days/week)	Body Weight (kg)	Transformed Dose (mg/kg/day)	Equivalent Human Dosage (mg/kg/day)	Incidence No. Responding/ No. Tested (or Examined)
0	0.250	0	0	0/50
100	0.250	71.4	10.6	1/50
200	0.225	142.9	20.5	8/50

Human $q_1^* = 7.9 \times 10^{-3}$ $(mg/kg/day)^{-1}$

APPENDIX C

Summary Table for Bromoform

	Species	Exposure	Effect	RfD or q_1^*	Reference
Inhalation Exposure					
Subchronic	ID	ID	ID	ID	ID
Chronic	ID	ID	ID	ID	ID
Carcinogenicity	ID	ID	ID	ID	ID
Oral Exposure					
Subchronic	rat	NOEL: 25 mg/kg/day, 5 days/week for 13 weeks (17.9 mg/kg/day)	hepatocellular vacuolization	0.2 mg/kg/day or 13 mg/day for a 70 kg man	NTP, 1988
Chronic	rat	NOEL: 25 mg/kg/day, 5 days/week for 13 weeks (17.9 mg/kg/day) based on subchronic study	hepatocellular vacuolization based on subchronic study	0.02 mg/kg/day or 1.3 mg/day for a 70 kg man based on subchronic study	NTP, 1988
Carcinogenicity	rat	0, 100 or 200 mg/kg/day, 5 days/week for 103 weeks (0, 71.4 or 142.9 mg/kg/day)	adenomatous polyps or adenocarcinomas in the large intestine	$q_1^* = 7.9 \times 10^{-3}$ $(mg/kg/day)^{-1}$ based on internal dose	NTP, 1988
REPORTABLE QUANTITIES					
Based on chronic toxicity:	1000				NTP, 1988
Based on carcinogenicity:	100				NTP, 1988

ID = Insufficient data